

Factive (Gemifloxacin)

**For the Treatment of Acute Exacerbations of Chronic Bronchitis and
Community-Acquired Pneumonia**

Briefing Document

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TABLE OF CONTENTS

LIST OF TABLES	6
LIST OF FIGURES	10
LIST OF ABBREVIATIONS	11
1. EXECUTIVE SUMMARY	14
2. INTRODUCTION	17
3. CHEMISTRY AND MANUFACTURING	18
4. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY	19
4.1 Pharmacology: Mechanism of Action	19
4.2 Toxicology	19
5. HUMAN PHARMACOKINETICS	22
6. MICROBIOLOGY	24
6.1 Enhanced Potency Against Key Respiratory Pathogens	24
6.2 Dual Enzyme Targeting	27
6.3 Pharmacokinetic/Pharmacodynamic Parameters Correlate for Predicting Efficacy and Lack of Resistance Generation	28
6.3.1 Gemifloxacin Activity in the Face of Rising Antibiotic Resistance	30
6.3.2 In Vitro Data on Gemifloxacin Activity Against Resistant <i>S. Pneumoniae</i>	31
6.3.2.1 In Vitro Data on <i>S. Pneumoniae</i> Resistant to Quinolones	31
6.3.2.2 In Vivo Models of <i>S. Pneumoniae</i> Respiratory Tract Infection	35
6.3.3 Gemifloxacin and Likelihood of Resistance Development	37
7. REVIEW OF GEMIFLOXACIN EFFICACY IN ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS	39
7.1 Background and Rationale	39
7.2 Overview of Gemifloxacin Clinical Program in AECB	40
7.3 Demography and Patient Characteristics	43
7.4 Results of AECB Clinical Studies	47
7.4.1 Overall Success Rates	47
7.4.2 Eradication of <i>H. influenzae</i>	48
7.4.3 Subgroup Analyses	49
7.4.4 Supportive Clinical Studies in AECB - Studies 069 and 207	50
7.4.5 Results of Eradication of Key Pathogens Associated with AECB	51

7.4.6 Other Studies in AECB	52
7.4.6.1 Long-Term Follow-up of Study 068 (Study 139)	52
7.4.6.2 Study 112	53
7.5 Conclusions from AECB studies	53
8. REVIEW OF GEMIFLOXACIN EFFICACY IN COMMUNITY-ACQUIRED PNEUMONIA	55
8.1 Background and Rationale	55
8.2 Overview of Gemifloxacin Studies in CAP	56
8.3 Demographic and Baseline Characteristics	59
8.4 Results of CAP Clinical Studies	66
8.4.1 Overall Success Rates	66
8.4.2 Subgroup Analysis	71
8.4.2.1 Efficacy by Demographic Characteristics	71
8.4.2.2 Efficacy in Severe CAP, Hospitalized Patients, Bacteremia	72
8.4.2.3 Efficacy of a Planned Treatment Duration of 7 Days of Gemifloxacin	73
8.4.3 Eradication of Key Pathogens in Gemifloxacin CAP Studies	76
8.4.4 Gemifloxacin in CAP Due to PRSP	77
8.4.5 Efficacy of Gemifloxacin Treatment in CAP due to Macrolide Resistant <i>S. Pneumoniae</i>	78
8.4.6 Efficacy of Gemifloxacin Treatment in CAP due to Cefuroxime-Resistant <i>S. Pneumoniae</i>	78
8.4.7 Efficacy of Gemifloxacin in CAP Due to <i>S. Pneumoniae</i> Resistant to Ciprofloxacin	78
8.5 Conclusions in CAP	79
9. REVIEW OF SAFETY	80
9.1 Demographics	80
9.2 Patient Adverse Event Profile	81
9.2.1 Overall	81
9.2.2 Serious Adverse Events (SAEs)	84
9.2.3 Withdrawals Due to AEs	84
9.2.4 Deaths	84
9.3 Rash	84
9.3.1 Rash by Duration of Treatment	87
9.3.2 Time to Onset of Rash	88
9.3.3 Duration of Rash	89
9.3.4 Severity of Rash	90
9.3.5 Rash by Gender	91
9.3.6 Rash by Age, Gender, and Planned Treatment Duration	91
9.3.7 Rash by Oral Contraceptive Use or Hormone Replacement Therapy	93
9.3.8 Rash by Indication	94

9.3.9	Previous Gemifloxacin Exposure	95
9.3.10	Previous Quinolone Exposure	96
9.3.11	Subsequent Exposure to Another Quinolone	96
9.3.12	Systemic Signs in Association with Rash	97
9.3.13	Immune System Reactions in Association With Rash	99
9.4	Study 344	99
9.4.1	Study Design	100
9.4.2	Evaluation Criteria	102
9.4.3	Study Population	103
9.4.4	Incidence of Rash	103
9.4.5	Description and Characteristics of Rash	106
9.4.6	Histopathological Review of Rash	111
9.4.7	Pharmacokinetic Evaluation	112
9.4.8	Laboratory Tests	114
9.4.9	Conclusions from Study 344	115
9.5	Cardiac Safety	116
9.5.1	QTc Interval Changes	116
9.5.2	Clinical Pharmacology Studies	117
9.5.2.1	Mean QTc Change	117
9.5.2.2	QTc Values Outside Pre-set Reference Limits	118
9.5.3	Patient Studies	119
9.5.3.1	Mean QTc Change	121
9.5.3.2	Distribution of On-Therapy Changes in QTc in Patients	123
9.5.3.3	Treatment-Emergent Qualitative Changes in ECG Waveform Morphology	125
9.5.3.4	Clinical Conditions Associated with Arrhythmias	126
9.5.4	Patients Receiving Intravenous Gemifloxacin in Phase III Studies	129
9.5.4.1	Effects on QTc	129
9.5.4.2	QTc Prolongation for Other Quinolones	130
9.5.5	Conclusion	132
9.6	Hepatic Safety	132
9.6.1	Independent Review of Liver Findings	135
9.7	Safety Conclusions	136
10.	DISCUSSION	137
11.	RISK MANAGEMENT PLAN	140
11.1	Introduction	140
11.2	Spontaneous Reports	140
11.3	Off Label Use Minimization	140
11.4	Phase 4 Study	141
12.	CONCLUSION	142

13. REFERENCES..... 143

APPENDIX 1: RETROSPECTIVE DRUG UTILIZATION STUDY TO ASSESS THE
LIKELY PREVALENCE OF GEMIFLOXACIN ASSOCIATED RASH IN
FEMALES LESS THAN 40 YEARS OF AGE RECEIVING GEMIFLOXACIN
FOR GREATER THAN 7 DAYS UTILIZING FIXED DOSAGE PACKAGING 148

LIST OF TABLES

Table 1: Concentrations of Gemifloxacin after 5 Daily Doses of 320 mg	23
Table 2: <i>In Vitro</i> Activity of Gemifloxacin and Comparators Against <i>S. Pneumoniae</i> Isolates	25
Table 3: <i>In Vitro</i> Activity of Gemifloxacin and Comparators Against 290 <i>H. influenzae</i> Isolates Collected from 16 U.S. Hospitals	26
Table 4: <i>In Vitro</i> Activity of Gemifloxacin and Comparators Against 205 <i>M. catarrhalis</i> Isolates Collected from 16 U.S. Hospitals	26
Table 5: Activity of Gemifloxacin and Comparators Against Atypical Organisms	26
Table 6: MICs (µg/mL) of Ciprofloxacin-Selected <i>S. Pneumoniae</i> Mutants	28
Table 7: Susceptibility of Ciprofloxacin-Intermediate and -Resistant <i>S. Pneumoniae</i> to Fluoroquinolones and Comparators	28
Table 8: Comparative Free Drug Pharmacokinetic/Pharmacodynamic Parameters for <i>S. pneumoniae</i>	29
Table 9: Proposed MIC Breakpoints	30
Table 10: <i>In Vitro</i> Activity of Gemifloxacin and Comparators Against Penicillin Non-Susceptible Isolates of <i>S. Pneumoniae</i>	31
Table 11: <i>In Vitro</i> Activity of Gemifloxacin and Comparators Against Isolates of Macrolide Resistant <i>S. Pneumoniae</i>	31
Table 12: <i>In Vitro</i> Activity of Gemifloxacin and Comparators Against Isolates of Ciprofloxacin Non-Susceptible <i>S. Pneumoniae</i>	32
Table 13: <i>In Vitro</i> Activity of Gemifloxacin and Comparators Against Isolates of Levofloxacin Non-Susceptible <i>S. Pneumoniae</i>	32
Table 14: Phase II Results: <i>In Vitro</i> Activity (MIC µg/mL) of Gemifloxacin and Comparative Agents Against 77 <i>S. pneumoniae</i> Isolates Non-Susceptible to Levofloxacin (MIC >2 µg/mL)	33
Table 15: Efficacy of Gemifloxacin against Respiratory Tract Infections in the Rat Caused by <i>S. Pneumoniae</i> with Differing <i>In Vitro</i> Susceptibilities	36
Table 16: MICs of Gemifloxacin, Moxifloxacin, and Gatifloxacin against <i>S. pneumoniae</i> Isolates used in the Rat RTI Model	36
Table 17: Efficacy of Gemifloxacin, Moxifloxacin, and Gatifloxacin against <i>S. pneumoniae</i> in the Rat RTI Model	37
Table 18: Acute Exacerbation of Chronic Bronchitis: Principal, Supportive, and Other Studies	41
Table 19: AECB Severity Criteria (Ball and Make 1998)	43
Table 20: Demographic and Baseline Characteristics: AECB Principal Studies 068, 070, and 212 (Clinical PP)	45
Table 21: Number (%) of Patients with Key Pathogens Associated with AECB at Screening: Principal AECB Studies	46
Table 22: Clinical Response at Follow-Up (Test of Cure): Principal AECB Studies	47
Table 23: Bacteriological Response at Follow-Up (Test of Cure): Principal AECB Studies	48

<u>Table 24: Number (%) of Patients with Response of Bacterial Persistence by Day in AECB Study 068</u>	49
<u>Table 25: Time to Discharge from Hospital (Clinical ITT population) in Study 207</u>	51
<u>Table 26: Pre-Therapy Pathogens Eradicated or Presumed Eradicated at End of Therapy and Follow-Up: AECB Combined Studies</u>	52
<u>Table 27: The Proportions of Patients with No Recurrences after Resolution of the Initial Episode of AECB in Study 139 at Each Visit</u>	53
<u>Table 28: CAP: Controlled and Uncontrolled Studies of Gemifloxacin</u>	57
<u>Table 29: Demographic and Baseline Characteristics: CAP Combined Datasets (Clinical PP Follow-Up Population)</u>	62
<u>Table 30: Demographic and Baseline Characteristics: CAP Combined Datasets (ITT Population)</u>	63
<u>Table 31: Assessment of CAP Severity: Stratification of Risk Score</u>	64
<u>Table 32: Point Scoring System for Assignment to Risk Classes II, III, IV, and V</u>	65
<u>Table 33: Summary of Clinical Success Rates at Follow-Up: CAP Studies</u>	67
<u>Table 34: Summary of Bacteriological Response at Follow-Up: CAP Studies</u>	68
<u>Table 35: Summary of Radiological Success Rates at Follow-Up: CAP Studies (Clinical PP Population)</u>	68
<u>Table 36: Rates of Clinical and Bacteriological Success at Follow-Up for Patients with Severe CAP: CAP Combined All Studies</u>	72
<u>Table 37: Rates of Clinical and Bacteriological Success at Follow-Up for Patients Hospitalized at Screening: CAP Combined All Studies</u>	72
<u>Table 38: Rates of Clinical and Bacteriological Success at Follow-Up for Patients who were Bacteremic at Screening: CAP Combined All Studies</u>	73
<u>Table 39: Rates of Clinical and Bacteriological Success at Follow-Up by Planned Treatment Duration: CAP Combined Controlled Studies¹</u>	74
<u>Table 40: Rates of Clinical and Bacteriological Success at Follow-Up for Patients with Severe CAP by Planned Duration of Treatment: CAP Combined All Studies¹</u>	75
<u>Table 41: Rates of Clinical and Bacteriological Success at Follow-Up for Hospitalized Patients by Planned Duration of Treatment: CAP Combined All Studies¹</u>	75
<u>Table 42: Rates of Clinical and Bacteriological Success at Follow-Up for Patients with Bacteremia by Planned Duration of Treatment: CAP Combined All Studies¹</u>	76
<u>Table 43: Bacteriological Eradication and Clinical Cure Rates for <i>S. Pneumoniae</i> Pathogens by Gemifloxacin MIC - CAP</u>	77
<u>Table 44: Demographic Characteristics in Clinical Studies (Gemifloxacin 320 mg versus All Comparators)</u>	81
<u>Table 45: Number (%) of Patients With the Most Frequently Occurring ($\geq 1\%$) Adverse Experiences in Either Treatment Group During the Interval On-Therapy Plus 30 Days Post-Therapy</u>	83
<u>Table 46: Incidence of Adverse Experiences of Rash for Both Treatment Groups</u>	85
<u>Table 47: Reason for Gemifloxacin Rash SAEs</u>	86
<u>Table 48: Episodes of Facial Edema in Clinical Trials</u>	87

Table 49: Number (%) of Patients with Rash by Duration of Treatment	88
Table 50: Maximum Severity of Rash By Duration of Exposure	91
Table 51: Number (%) of Patients with Rash by Age and Gender According to Planned Treatment Duration	92
Table 52: Number (%) of Female Patients with Rash by Oral Contraceptive Use	93
Table 53: Number (%) of Female Patients with Rash by HRT Use	94
Table 54: Patients with AECB with Rash On Therapy Plus 30 Days Post Therapy – Combined Population	95
Table 55: Patients with CAP with Rash On Therapy Plus 30 Days Post Therapy – Combined Population	95
Table 56: Point Estimates and 95% CI for Incidence of Rash in Part A	104
Table 57: Signs and Symptoms Associated with Rash in Part A	108
Table 58: Hepatic Markers in Part A	109
Table 59: Number (%) of Subject Sessions with Eosinophil Count Transitions, No Rash	110
Table 60: Number (%) of Subject Sessions with Eosinophil Count Transitions, Rash	110
Table 61: Summary Statistics for Day of Rash Onset in Part B	110
Table 62: Mean Change from Baseline in QTc Interval Following Repeated Dosing in Healthy Volunteers (Study 344)	117
Table 63: Number (%) of Healthy Volunteers with QTc >470msec On-Therapy, or Change in QTc >60msec from Baseline (Study 344)	119
Table 64: Distribution of Gender and Age of Patients with Paired QTc Recordings	119
Table 65: Proportion of Patients with Paired QTc Who had Co-morbid Conditions Known to Predispose to QTc Prolongation	120
Table 66: Number (%) of Patients with Selected Off-Therapy ECG Abnormalities	121
Table 67: Mean QTc Interval Change from Off-Therapy Value in Patients with Paired QTc Measurements	122
Table 68: Mean QTc Interval Change from Off-Therapy Value in Female Patients with Paired QTc Measurements	122
Table 69: Mean QTc Interval Change from Off-Therapy Value in Patients with Paired QTc Measurements, and Aged over 65 Years	122
Table 70: Mean QTc Interval Change from Off-Therapy Value in Patients with Paired QTc Measurements, and with Comorbid Conditions Known to Predispose to QTc Prolongation	123
Table 71: Mean QTc Interval Change from Off-Therapy Value in Patients with Paired QTc Measurements who Received Concomitant Therapy Associated with QTc Prolongation	123
Table 72: Number (%) of Patients with Changes in QTc from Off-Therapy Value in Patients with Paired QTc	124
Table 73: Number (%) of Patients with QTc Greater Than the Reference Range (>450 msec, Male or >470 msec, Female) in Patients with Paired QTc	124
Table 74: Number (%) of Patients with QTc >500 msec in Patients with Paired QTc	125
Table 75: Number (%) of Patients With Paired ECGs Showing Qualitative Changes in T	

[wave or S-T segment, and Treatment-Emergent U Wave](#) 126

[Table 76: Number \(%\) of Patients with Syncope, Convulsions, Sudden Death, and Cardiac Arrest \(All-Exposed Population\)](#)..... 126

[Table 77: Change in QTc From Off-Therapy Baseline to On-Therapy \(50-60 Minutes\) For Patients With a Paired QTc Recording: Intravenous Population](#) 130

[Table 78: QTc Interval Prolongation of Quinolone Antibiotics](#) 131

[Table 79: Number \(%\) of Patients with Liver Clinical Chemistry Values Outside the F2F3 Range at the On-Therapy and End-of-Therapy Visits](#) 133

[Table 80: Number \(%\) of Patients with Treatment-Emergent Liver Function Tests within the Specified Ranges at the On-Therapy and End-of-Therapy Visits](#)..... 134

LIST OF FIGURES

Figure 1: Gemifloxacin Mesylate	18
Figure 2: IC₅₀ for hERG Inhibition vs. Prolongation of APD₉₀ (100 μM, 1 Hz) for Gemifloxacin and Comparator Quinolones	20
Figure 3: Activity of Gemifloxacin and Comparator Quinolones Against <i>S. pneumoniae</i> Demonstrating Second Step Mutations in the QRDR	34
Figure 4: Fluoroquinolone Killing of a Quinolone-Resistant <i>S. Pneumoniae</i> Isolate (17012) Simulating Free AUC₂₄/MIC Ratios	35
Figure 5: AECB Clinical Response at Follow-Up: Treatment Differences and 95% Confidence Intervals Clinical PP and ITT Population	48
Figure 6: Treatment Differences and 95% Confidence Intervals for Clinical Response Rates at Follow-Up: Individual Controlled CAP Studies (011, 012, 049, and 185) and Combined Analysis	69
Figure 7: Treatment Differences and 95% Confidence Intervals for Bacteriological Response Rates at Follow-Up: Individual Controlled CAP Studies (011, 012, 049, and 185) and Combined Analysis	70
Figure 8: Treatment Differences and 95% Confidence Intervals for Radiological Response Rates at Follow-Up: Individual Controlled CAP Studies (011, 012, 049, and 185)	70
Figure 9: Time to Onset of Rash from Start of Study Medication	89
Figure 10: Duration of Rash	90
Figure 11: Study Design for Study 344	101
Figure 12: Subject Disposition in Part A and Part B	104
Figure 13: Gemifloxacin-Associated Rash in Part A: Distribution for Days to Onset	106
Figure 14: Gemifloxacin-Associated Rash in Part A: Distributions for Duration of Rash	107
Figure 15: Gemifloxacin-Associated Rash in Part A: Severity and Body Surface Area Affected	108
Figure 16: AUC for Gemifloxacin and N-Acetyl Gemifloxacin in Subjects with and without Rash (Box-Whisker Plot)	113
Figure 17: Pharmacokinetic Parameter Ratios in Subjects with and without Rash (Box-Whisker Plots)	114
Figure 18: Highest Observed Change in QTc Interval (ΔQTc) vs. Corresponding Maximum Plasma Gemifloxacin Concentration (C_{max}) for Subjects Given a Single or Repeated Dose of Gemifloxacin in Study 344	118

LIST OF ABBREVIATIONS

ABS	acute bacterial sinusitis
ADP ₉₀	action potential duration at 90% repolarization
AE(s)	adverse experience(s)
AECB	acute exacerbation of chronic bronchitis
Alk phos	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
AUC ₂₄	area under the concentration-time curve to 24 hours
bid	twice daily
<i>C. pneumoniae</i>	<i>Chlamydia pneumoniae</i>
CAP	community acquired pneumonia
CAPD	continuous ambulatory peritoneal dialysis
CFU	colony form units
CI	confidence interval
Cipro	ciprofloxacin
C _{max}	maximum concentration
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
CrCL	creatinine clearance
CRF	case report forms
CRSP	clarithromycin-resistant <i>S. pneumoniae</i>
cUTI	complicated urinary tract infection
d	days
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ECG	electrocardiogram
ELF	epithelial lining fluid
ERSP	erythromycin-resistant <i>S. pneumoniae</i>
FDA	Food and Drug Administration
FEV1	forced expiratory volume in one second
Gemi	gemifloxacin
GGT	γ-glutamyl transpeptidase
GMT	geometric mean titer
g	gram
h	hour
<i>H. influenzae</i>	<i>Haemophilus influenzae</i>

<i>H. parainfluenzae</i>	<i>Haemophilus parainfluenzae</i>
HRT	hormone replacement therapy
IDSA	Infectious Disease Society of America
ISE	integrated summary of efficacy
ITT	intent-to-treat
IU	international unit
IV	intravenous
<i>K. pneumoniae</i>	<i>Klebsiella pneumoniae</i>
kg	kilograms
<i>L. pneumophila</i>	<i>Legionella pneumophila</i>
LDH	lactate dehydrogenase
LFT	liver function test
LGLS	LG Life Sciences, Ltd.
<i>M. catarrhalis</i>	<i>Moraxella catarrhalis</i>
<i>M. pneumoniae</i>	<i>Mycoplasma pneumoniae</i>
MBC	minimum bactericidal concentration
mg	milligram
MIC	minimum inhibitory concentration
MIC ₅₀	minimum concentration of antibiotic needed to inhibit the growth of 50% of the bacteria strains tested in culture
MIC ₉₀	minimum concentration of antibiotic needed to inhibit the growth of 90% of the bacteria strains tested in culture
min	minutes
mL	milliliters
MPC	mutant prevention concentrations
msec	millisecond
N	number
NCCLS	National Committee for Clinical Laboratory Standards
NDA	New Drug Application
NGU	non-gonococcal urethritis
Nrash	no rash
NSAID	nonsteroidal anti-inflammatory drug
OC	oral contraceptive therapy
od	once daily
<i>P. aeruginosa</i>	<i>Pseudomonas aeruginosa</i>
PDR	Physicians' Desk Reference
PID	patient identification
PK	pharmacokinetic
Plc	placebo
PO	per os; orally
PP	per protocol

PRSP	penicillin-resistant <i>S. pneumoniae</i>
QRDR	quinolone resistance-determining region
ref	reference
RTI	respiratory tract infection
<i>S. aureus</i>	<i>Staphylococcus aureus</i>
<i>S. pneumoniae</i>	<i>Streptococcus pneumoniae</i>
SAE	serious adverse experience
SB	SmithKline Beecham
SD	standard deviation
SGOT (AST)	serum glutamate-oxaloacetate transaminase
SGPT (ALT)	serum glutamate-pyruvate transaminase
SJS	Stevens-Johnson syndrome
$t_{1/2}$	half-life
TEN	toxic epidermal necrolysis
tid	three times daily
μg	micrograms
ULN	upper limit of normal
uUTI	uncomplicated urinary tract infection
uSSSI	uncomplicated skin and skin structures infection
WBC	white blood cells
yr	year

1. EXECUTIVE SUMMARY

This New Drug Application (NDA) seeks approval of gemifloxacin (Factive[®]) for the treatment of acute exacerbations of chronic bronchitis (AECB) and community-acquired pneumonia (CAP) in patients 18 years of age or older. The proposed dosing regimen consists of 320 mg administered orally once daily for 5 (AECB) or 7 (CAP) days.

Gemifloxacin is a synthetic, broad-spectrum, fluoroquinolone antibacterial agent. It is unique in its dual targeting capacity - achieving plasma concentrations adequate to inhibit both topoisomerase IV and gyrase - distinguishing it from the other fluoroquinolones, which inhibit either but not both targets. Gemifloxacin has excellent *in vitro* activity against both Gram-positive organisms and Gram-negative organisms, including potent antibacterial activity against respiratory tract infection pathogens, particularly *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. It also has excellent activity against the atypical organisms, *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.

With the continuing increase in the prevalence of community-acquired respiratory pathogens with resistance to a variety of antimicrobial agents, more potent agents with improved activity, particularly versus *S. pneumoniae*, are clearly needed. Gemifloxacin offers a number of advantages compared with other antibacterial agents in the treatment of respiratory tract infections.

Gemifloxacin is the most potent agent *in vitro*, compared with commercially available antimicrobials, against *S. pneumoniae*, including isolates resistant to β -lactams and macrolides. Increasingly physicians are turning to the fluoroquinolones for the treatment of community respiratory infections. However resistance is now growing to this class. Gemifloxacin is the only fluoroquinolone to retain activity against *S. pneumoniae* resistant to other fluoroquinolones. It also has the lowest potential for development of resistance of all quinolones currently available. The clinical significance of quinolone-resistant *S. pneumoniae* has been highlighted in recent reports of levofloxacin-resistant pneumococcal pneumonia, leading to treatment failure and death. In these studies, all baseline isolates collected were susceptible to gemifloxacin, and isolates from 5 of 8 patients remained susceptible to gemifloxacin following emergence of levofloxacin resistance (Davidson 2002; Low 2002). The last isolate, collected from a patient who died, was gemifloxacin susceptible. All levofloxacin-resistant organisms were either resistant or intermediate to moxifloxacin and gatifloxacin.

In clinical studies, gemifloxacin has proven clinical and bacteriological efficacy for 5-day treatment of AECB. Gemifloxacin has been demonstrated to be effective in the eradication of the pathogens associated with AECB. Bacterial eradication by gemifloxacin is also very rapid. Long-term clinical benefits experienced by patients treated with gemifloxacin include prolonged

exacerbation-free intervals, the potential for fewer hospitalizations, and shorter time to discharge in patients requiring hospitalization.

In the treatment of CAP, oral gemifloxacin 320 mg once daily has demonstrated clinical and bacteriological efficacy when given for either 7 or 14 days. With a 7-day regimen, treatment was shorter than the regimens for many comparators. Gemifloxacin treatment for 7 days was effective for all severities of CAP, including patients with severe CAP, hospitalized patients, and patients with bacteremia.

Gemifloxacin was effective in the treatment of CAP due to penicillin-resistant *S. pneumoniae* (PRSP), macrolide-resistant *S. pneumoniae* (MRSP), cephalosporin-resistant *S. pneumoniae* (CRSP), and ciprofloxacin non-susceptible and ciprofloxacin-resistant *S. pneumoniae*. Treatment with oral gemifloxacin was demonstrated to be as effective as intravenous (IV) ceftriaxone/oral cefuroxime in hospitalized patients. Overall, the results of the CAP clinical program have demonstrated that gemifloxacin, with just 7 days of treatment, can provide appropriate coverage when used as an empirical therapy for the treatment of CAP in the prevailing environment of resistance to traditional antibacterial agents.

Overall, gemifloxacin 320 mg was well tolerated in clinical studies. Use of gemifloxacin was associated with small, measurable changes in the electrocardiographic QTc interval. However, these prolongations were not clinically meaningful. Because gemifloxacin has no drug interaction issues, specifically a lack of cytochrome P450, administration of co-medications that can potentiate QTc interval changes with other drugs should not be problematic. Gemifloxacin treatment was not associated with any consistent liver clinical chemistry finding. Treatment-emergent changes of potential clinical concern in liver values were very infrequent. The incidence of rash was higher for the gemifloxacin group than for the all-comparators group. However, most cases of rash were of mild or moderate intensity, and there were no clinically significant complications.

At the request of the FDA, a landmark study (Study 344), involving 1,011 young adult females, was conducted to further evaluate and characterize the gemifloxacin-associated rash. The characteristics of rash observed in the study were consistent with those of rash observed in the clinical trial program. There were no reports of serious cutaneous reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis or any other significant sequelae. The nature of the rash was consistent with a typical, exanthematous drug eruption. Typically, the pathology (routine histopathology, immunofluorescence, and immunohistochemistry) seen was a mild, superficial, perivascular lymphocytic reaction, i.e., the classic pathology of a delayed Type IV sensitivity mild drug rash. No pathology associated with more severe skin reactions to drugs was evident.

Gemifloxacin, by virtue of its inherent *in vitro* potency, pharmacokinetics, and proven clinical efficacy against both antibiotic sensitive and resistant strains of bacteria responsible for common respiratory diseases, offers unique benefits, while possessing a risk profile equivalent to that of currently marketed antibiotics, including other fluoroquinolones. Gemifloxacin represents an important new therapeutic option for treatment of AEBC and CAP, particularly those cases involving resistant organisms.

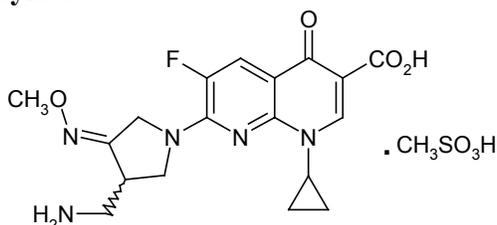
2. INTRODUCTION

The product described in this document is a new, synthetic, broad-spectrum, fluoroquinolone antibacterial agent known as gemifloxacin (Factive[®], SB-265805). Clinical testing of gemifloxacin began in 1997. In December 1999, a New Drug Application (NDA) for use of gemifloxacin was submitted to the Food and Drug Administration (FDA). A non-approvable letter was issued in December 2000. In 2001, the sponsor conducted additional studies designed in conjunction with the FDA and also conducted additional analyses to address FDA questions. In October 2002, the NDA was resubmitted for the use of gemifloxacin for the treatment of acute exacerbations of chronic bronchitis (AECB) and community-acquired pneumonia (CAP). This briefing document provides a short background on AECB and CAP, and summarizes key chemistry and manufacturing, nonclinical, microbiological, and clinical information as presented in the NDA application.

3. CHEMISTRY AND MANUFACTURING

Gemifloxacin is a synthetic fluoronaphthyridine antibiotic (Figure 1). The molecular formula of gemifloxacin mesylate is $C_{18}H_{20}FN_5O_4 \cdot CH_4O_3S$.

Figure 1: Gemifloxacin Mesylate



The final dosage form is a tablet containing 320 mg gemifloxacin as gemifloxacin mesylate sesquihydrate. The molecular weight of the free base is 76.0% of the gemifloxacin mesylate sesquihydrate. The dose strength and label claim are reported as the free base.

A 320 mg white film-coated oval debossed tablet with break lines on both faces is to be supplied in fixed dose blister packs of 5 and 7 tablets.

4. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

The primary pharmacology, safety pharmacology, general (oral and intravenous [IV]) toxicity, reproductive and genetic toxicity, phototoxicity, photomutagenicity, photocarcinogenicity, and antigenicity of gemifloxacin have been evaluated. Additional studies were conducted to establish the mechanism of hepatic findings and clastogenicity, and to characterize any risk of QTc prolongation.

4.1 Pharmacology: Mechanism of Action

Fluoroquinolones are potent antibacterial agents that act by inhibiting deoxyribonucleic acid (DNA) synthesis through inhibition of the bacterial type II topoisomerase enzymes, DNA gyrase and topoisomerase IV, both of which are essential for bacterial growth (Wang 1996; Drlica and Zhao 1997). DNA gyrase, encoded by *gyrA* and *gyrB* genes, catalyzes adenosine triphosphate (ATP)-dependent DNA supercoiling during DNA replication (Wang 1996; Drlica and Zhao 1997). Topoisomerase IV (specified by *parC* and *parE* genes) facilitates the separation of replicating DNA (Wang 1996; Drlica and Zhao 1997).

The enhanced Gram-positive activity of gemifloxacin, relative to other fluoroquinolones, is due to its potent activity against both topoisomerase IV (SB-265805/RSD-1014CH/1; SB265805/RSD-1010MF/1) and DNA gyrase. None of the commercially available quinolones bind to both sites at the plasma concentrations achieved at therapeutic dose. This superior activity is retained even against many fluoroquinolone-resistant strains for gemifloxacin (SB265805/RSD-1010MF/1).

4.2 Toxicology

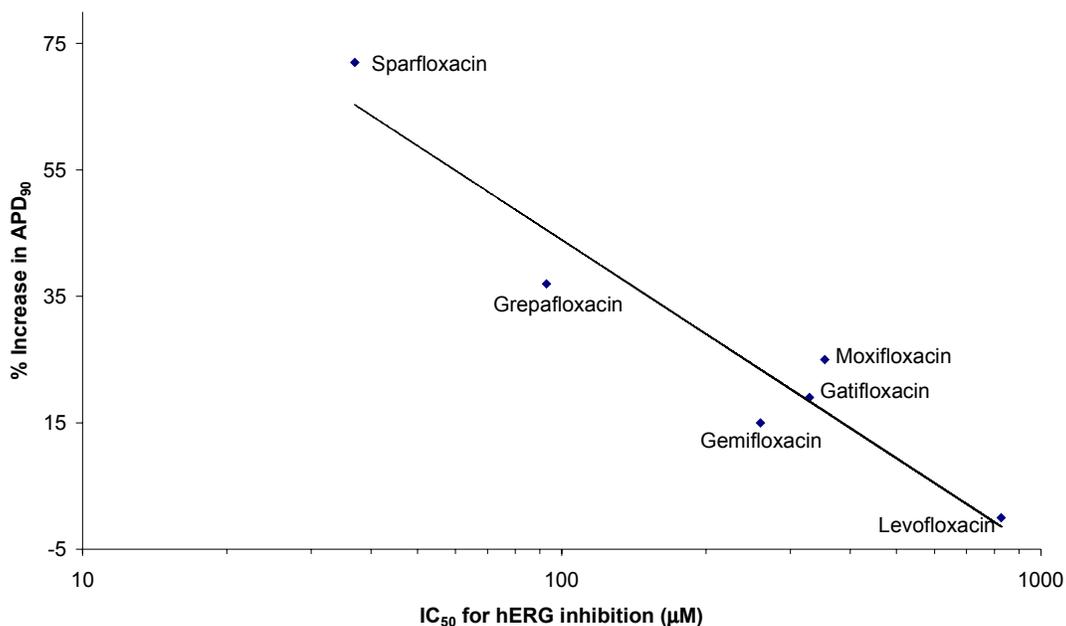
Gemifloxacin produces effects in nonclinical studies that are generally characteristic of the fluoroquinolone antibiotic class. In studies of class effects of potential clinical concern conducted against fluoroquinolone comparators, gemifloxacin's capacity to cause phototoxicity or adverse central nervous system (CNS) reactions, including its binding potency at GABA receptors, was shown to be very low.

Key findings include a weak potential to provoke QTc prolongation and hepatotoxicity in dogs.

In dogs, QTc was unaffected at approximately 5.5 times the mean human plasma maximum concentration (C_{max}) (320 mg PO) following oral administration of gemifloxacin, but QTc was mildly and reversibly prolonged following a 30-minute IV infusion (plasma C_{max} at the no-effect dose was approximately 3 times the human value).

Gemifloxacin was compared with other fluoroquinolones and macrolides in *in vitro* Purkinje fibre and hERG assay systems considered to reflect potential for prolongation of QTc. In dog Purkinje fibers, increases in action potential duration at 90% repolarization (APD₉₀) (1 Hz) at 100 µM were caused by sparfloxacin (72%), grepafloxacin (37%), moxifloxacin (25%), gatifloxacin (19%), and gemifloxacin (15%). Levofloxacin increased the APD₉₀ by 23% only at 1000 µM. There is evidence that greater magnitude of effect on action potential duration or potency of inhibition of key cardiac ion channels is alerting for increased likelihood of QTc prolongation. Prolongation of APD₉₀ has been associated with inhibition of the rapidly activating delayed rectifier K⁺ current, I_{Kr}, encoded by the human hERG gene. IC₅₀ values for inhibition of hERG expressed in a kidney cell line were: sparfloxacin (37 µM), grepafloxacin (93 µM), gemifloxacin (260 µM), gatifloxacin (329 µM), moxifloxacin (354 µM), and levofloxacin (827 µM). Increases in APD₉₀ correlated with inhibition of hERG (Figure 2). Gemifloxacin had only a minor effect in both *in vitro* systems even at a concentration (100 µM), approximately 30 times the mean C_{max} in humans after a 320 mg oral dose. On the basis of the overall investigational package, gemifloxacin is concluded to have a low potential to cause clinically significant QTc prolongation in humans.

Figure 2: IC₅₀ for hERG Inhibition vs. Prolongation of APD₉₀ (100 µM, 1 Hz) for Gemifloxacin and Comparator Quinolones



Hepatotoxicity in dogs showed the key characteristics of cholate stasis, with local deposition of gemifloxacin-related material in intrahepatic bile vessels (verified spectroscopically), reactive biliary cell changes, and subsequent bile-mediated hepatocellular involvement, predominantly periportal. These findings are distinct from the pattern of centrilobular necrosis produced by typical hepatocellular toxicants, including trovafloxacin. Reversibly altered activities of plasma alanine aminotransferase (ALT) and alkaline phosphatase (alk phos) acted as well-established markers of these effects. Further studies provided evidence of the critical solubility threshold dependency of gemifloxacin deposition in bile duct lumina. Therefore the most relevant determinant of cholate stasis will be the rate of presentation of drug to liver vs. the rate of clearance, including into bile. Even a conservative comparative analysis of bioavailability and biliary excretion of gemifloxacin, bile flow, biliary pH, and solubility of gemifloxacin indicates that humans are relatively protected by a lesser biliary drug burden, and by bile pH favoring maintenance of gemifloxacin in solution.

It is concluded that when coupled with the overall profile in humans, the results of the nonclinical safety studies are consistent with gemifloxacin's clinical use.

5. HUMAN PHARMACOKINETICS

The absolute bioavailability of gemifloxacin following oral administration in healthy volunteers is, on average, 71%, and is limited by the extent of absorption rather than by significant first-pass metabolism. Following a single dose oral administration of gemifloxacin to man, maximum serum concentrations were generally observed between 0.5 and 2.0 hours post-dose. Thereafter, concentrations generally declined in an apparently biexponential manner, with a terminal phase half-life ($t_{1/2}$) of approximately 8 hours. The pharmacokinetics of gemifloxacin were approximately linear over the dose range 20 to 800 mg. Following repeated administration of gemifloxacin, there was minimal accumulation of gemifloxacin at doses up to 640 mg once daily in young subjects and up to 480 mg once daily in the elderly. Urinary excretion of gemifloxacin generally accounted for 20% to 40% of the administered dose. The *in vitro* binding of gemifloxacin to plasma proteins was low in man (approximately 70%). A high fat breakfast had no clinically relevant effect on the bioavailability of gemifloxacin at doses of 320 and 640 mg and thus, gemifloxacin can be administered without regard to food.

Gemifloxacin has a low potential for cytochrome P450 enzyme-mediated drug-drug interactions. At steady state, gemifloxacin 320 mg once daily did not affect the repeat dose pharmacokinetics of oral theophylline, oral digoxin, or ethinylestradiol/levonorgestrel. Likewise, there was no pharmacodynamic effect on prothrombin time when gemifloxacin was co-administered with warfarin. Pharmacokinetic data indicated that either Maalox[®] or ferrous sulphate can be administered at least 3 hours prior to, and 2 hours or more after administration of gemifloxacin and that sucralfate can be administered at least 2 hours after gemifloxacin administration. Simultaneous administration of calcium carbonate resulted in a modest reduction (on average, 20%) in gemifloxacin area under the concentration-time curve (AUC) and C_{max} , whilst administration of calcium carbonate, either 2 hours before or 2 hours after gemifloxacin dosing showed no notable reduction in systemic exposure. Co-administration of gemifloxacin with omeprazole at steady state resulted in increases in $AUC_{(0-\infty)}$ and C_{max} of gemifloxacin (on average 10% and 11%, respectively) that are not clinically significant. Co-administration of cimetidine reduced renal clearance of gemifloxacin by, on average, 28%, compared to co-administration of gemifloxacin with placebo. However, this finding is unlikely to be of any clinical relevance, since only small increases in gemifloxacin AUC values (on average, 10%) were seen following co-administration with cimetidine. Co-administration of probenecid reduced the renal clearance of gemifloxacin (on average, 51%), but dose adaptation was not necessary. Results of population pharmacokinetic analysis of Phase III data indicated that none of the classes of concomitant medications investigated (diuretics, calcium, estradiol/ethinylestradiol, estrogens and progesterones) appear to alter the clearance of orally administered gemifloxacin.

Dosage adjustment of gemifloxacin is not considered necessary in patients with creatinine clearance ≥ 40 mL/min. However, for patients with creatinine clearance < 40 mL/min, including

hemodialysis and continuous ambulatory peritoneal dialysis (CAPD) patients, it is recommended that the clinical dose of gemifloxacin be halved (i.e., 160 mg once daily). Gemifloxacin was not notably cleared from patients during 4 hours of hemodialysis. Dosage adjustment is not required for elderly patients with good renal function (creatinine clearance ≥ 40 mL/min; see above). Dosage adjustment of gemifloxacin is also not considered necessary in patients with mild, moderate, or severe hepatic impairment (Child-Pugh A, B or C).

Gemifloxacin is extensively distributed into body tissues and fluids. Concentrations in bronchoalveolar macrophages, epithelial lining fluid, bronchial mucosa, and plasma after 5 daily doses of 320 mg gemifloxacin are summarized in Table 1.

Table 1: Concentrations of Gemifloxacin after 5 Daily Doses of 320 mg

Tissue	Concentration (mean \pm SD)	Ratio Compared with Plasma
Plasma	1.40 (0.442) $\mu\text{g/mL}$	---
Bronchoalveolar macrophages	107 (77) $\mu\text{g/g}$	90.5 (106.3)
Epithelial lining fluid	2.69 (1.96) $\mu\text{g/mL}$	1.99 (1.32)
Bronchial mucosa	9.52 (5.15) $\mu\text{g/g}$	7.21 (4.03)

SD = standard deviation

6. MICROBIOLOGY

Gemifloxacin is the most potent fluoroquinolone against *S. pneumoniae* and demonstrates excellent *in vitro* activity versus penicillin-, macrolide-, cephalosporin-, and quinolone-resistant strains. Gemifloxacin retains good activity against Gram-negative organisms and is active against atypical pathogens. In addition, the pharmacokinetic and pharmacodynamic properties of gemifloxacin, including oral bioavailability, a $t_{1/2}$ of approximately 8 hours, and a long post antibiotic effect (from 1 to >6 hours), indicate that it is appropriate for once daily oral dosing.

Key microbiological features of gemifloxacin include:

1. Enhanced potency against key respiratory pathogens
2. Dual targeting of DNA gyrase and topoisomerase IV enzymes
3. Excellent pharmacokinetic/pharmacodynamic correlates for predicting efficacy and lack of resistance generation

These attributes translate into demonstrable advantages for the physician in the treatment of CAP and AECB, particularly in the setting of antibiotic-resistant *S. pneumoniae*, the principal pathogen in CAP. Uniquely among the current quinolones, gemifloxacin demonstrates significant activity against the emerging problem of quinolone-resistant *S. pneumoniae*.

6.1 Enhanced Potency Against Key Respiratory Pathogens

Gemifloxacin has broad-spectrum *in vitro* antibacterial activity, including excellent activity against the key respiratory pathogens, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *L. pneumophila*, *C. pneumoniae*, and *M. pneumoniae*. It has the lowest minimum inhibitory concentrations (MICs) against *S. pneumoniae* when compared with ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin (Table 2).

Table 2: *In Vitro* Activity of Gemifloxacin and Comparators Against *S. Pneumoniae* Isolates

# of Isolates	Gemifloxacin		Ciprofloxacin		Levofloxacin		Gatifloxacin		Moxifloxacin	
	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)								
6257	0.032	0.047	NT	NT	0.75	1	NT	NT	NT	NT
550	0.015	0.03	1	2	1	1	0.25	0.5	0.12	0.25
1450	≤0.015	0.06	1	1	1	1	0.25	0.25	NT	NT

NT = not tested

The MICs of gemifloxacin against *H. influenzae* and *M. catarrhalis* are comparable to or lower than those of other quinolones tested (Table 3 and Table 4, respectively).

Table 3: *In Vitro* Activity of Gemifloxacin and Comparators Against 290 *H. influenzae* Isolates Collected from 16 U.S. Hospitals

Compound	MIC range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)
Gemifloxacin	≤0.001-0.03	0.004	0.008
Ciprofloxacin	0.004-0.03	0.015	0.015
Levofloxacin	≤0.004-0.12	0.015	0.015
Gatifloxacin	≤0.002-0.03	0.008	0.015
Moxifloxacin	0.004-0.12	0.015	0.03

Table 4: *In Vitro* Activity of Gemifloxacin and Comparators Against 205 *M. catarrhalis* Isolates Collected from 16 U.S. Hospitals

Compound	MIC range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)
Gemifloxacin	0.004-0.03	0.015	0.015
Ciprofloxacin	0.03-0.12	0.03	0.06
Levofloxacin	0.03-0.25	0.03	0.06
Gatifloxacin	0.015-0.12	0.03	0.03
Moxifloxacin	0.03-0.25	0.06	0.06

Moreover, gemifloxacin demonstrates excellent activity against atypical organisms, as shown in Table 5. It is also active against anaerobic isolates, with MICs ≤0.25 µg/mL against 78% of the isolates tested.

Table 5: Activity of Gemifloxacin and Comparators Against Atypical Organisms

Organism	MIC ₉₀ (µg/mL)						
	N	Gemifloxacin	Trovafoxacin	Levofloxacin	Ciprofloxacin	Clarithromycin	Doxycycline
<i>Legionella pneumophila</i>	85	0.015	≤0.004	0.015	0.03	0.06	NT
<i>Chlamydia pneumoniae</i>	20	0.25	1	1	NT	NT	0.06
<i>Mycoplasma pneumoniae</i>	130	0.12	0.25	0.5	NT	≤0.008	NT

The minimum bactericidal concentrations (MBCs) of gemifloxacin are comparable to its MICs against a panel of 139 clinical isolates including *S. pneumoniae*, *S. pyogenes*, and *H. influenzae*. These data demonstrate that gemifloxacin is a cidal agent.

In time-kill viability studies, gemifloxacin exhibited bactericidal activity against a range of Gram-positive and Gram-negative organisms, including *S. pneumoniae*, *H. influenzae*, *S. aureus*, *E. coli*, and *P. aeruginosa*. Such activity, usually a 3-log reduction in viable cell numbers, was comparable to that of other quinolones.

6.2 Dual Enzyme Targeting

Quinolones act by inhibiting the bacterial enzymes that control the topological state of DNA: DNA gyrase, encoded by the *gyrA* and *gyrB* genes, and topoisomerase IV, encoded by the *parC* and *parE* genes. These enzymes catalyze DNA supercoiling, relaxing, knotting, and catenation by a double strand breaking and resealing mechanism, and are essential for prokaryotic cellular replication.

In *S. pneumoniae*, the principal target of fluoroquinolone action appears to vary with the specific antibacterial agent. Topoisomerase IV seems to be the preferential target for ciprofloxacin and levofloxacin, whereas moxifloxacin and gatifloxacin primarily target the *gyrA* subunit of DNA gyrase. Gemifloxacin is the only dual targeting quinolone with therapeutically relevant activity against both of these targets. The IC₅₀ values for the binding of gemifloxacin to the *parC* and *gyrA* subunits of topoisomerase IV and DNA gyrase have been assessed in a number of studies, although there is no standardized methodology. A topoisomerase IV IC₅₀ of 1.2 µg/mL and a DNA gyrase IC₅₀ of 2 µg/mL for gemifloxacin has been reported (Study No. SB-265805/RSD-101MN5/1). The dual activity of gemifloxacin is best demonstrated in studies of well-characterized resistant strains of *S. pneumoniae*. Gillespie et al. (2002) and Zhanel et al. (2002) have demonstrated that while mono targeting quinolones are rendered ineffective by single step mutations in their preferred target, gemifloxacin retains activity against mutants with mutations in either or both targets (MIC ≤0.25 µg/mL), as shown in Tables 6 and 7.

Table 6: MICs (µg/mL) of Ciprofloxacin-Selected *S. Pneumoniae* Mutants

Mutation	MIC (µg/mL)			
	Gemifloxacin	Moxifloxacin	Levofloxacin	Ciprofloxacin
wild-type	0.016	0.064	0.038	0.5
<i>parC</i> S79Y	0.064	0.125	1.5	4.0
<i>parC</i> S79F	0.032	0.125	1.0	2.0
<i>parC</i> S79Y, <i>gyrA</i> S81Y	0.25	2.0	>32	>32
<i>gyrA</i> S81Y*	0.023	0.125	0.75	1.0
<i>parC</i> S79Y	0.064	0.125	1.0	6.0
<i>parC</i> S79Y	0.047	0.064	1.0	4.0

*Selected by gemifloxacin

Data represents the mean of three E-test results

Table 7: Susceptibility of Ciprofloxacin-Intermediate and -Resistant *S. Pneumoniae* to Fluoroquinolones and Comparators

Strain	MIC (µg/mL)							
	Cip	Levo	Gati	Moxi	Gemi	<i>ParC</i> Change	<i>GyrA</i> Change	Efflux
2680	2	1	0.5	0.25	0.03	No	No	No
4610	4	1	0.5	0.25	0.06	Yes	No	No
16702	4	1	0.5	0.25	0.06	No	No	Yes
18705	4	2	0.5	0.25	0.03	Yes	No	Yes
16701	16	8	4	2	0.25	Yes	Yes	No
17012	16	8	4	2	0.12	Yes	Yes	No
18410	16	8	4	2	0.12	Yes	Yes	No

Cip = ciprofloxacin; Gati = gatifloxacin; Gemi =gemifloxacin; Levo = levofloxacin; Moxi = moxifloxacin

The high affinity of gemifloxacin for both of these targets accounts for its extremely high potency and, more critically, for its continued activity against quinolone-resistant *S. pneumoniae*. This is an important advantage, given that quinolone resistance is emerging at an alarming rate in the U.S. (Ferraro 2002).

6.3 Pharmacokinetic/Pharmacodynamic Parameters Correlate for Predicting Efficacy and Lack of Resistance Generation

Pharmacokinetic/pharmacodynamic (PK/PD) parameters predict the potential for efficacy, bacterial eradication and development of resistance with antimicrobial therapy.

Fluoroquinolones exhibit concentration-dependent killing and pharmacodynamic studies of fluoroquinolones in animal infection models and in human trials have indicated that the primary

fluoroquinolones in animal infection models and in human trials have indicated that the primary determinant of efficacy is the AUC_{24}/MIC_{90} ratio. The target ratio necessary to achieve maximal bacteriological efficacy in *S. pneumoniae* infections, for the existing quinolones, is 25-30. The C_{max}/MIC ratio has also been shown to predict efficacy and is being increasingly accepted to also correlate with a low potential for development of resistance. A target C_{max}/MIC ratio of 10 predicts a high probability of efficacy and a low potential for development of resistance.

Gemifloxacin has the highest free drug AUC_{24}/MIC_{90} ratio compared to other quinolones used to treat respiratory tract infections (levofloxacin, gatifloxacin, and moxifloxacin) (Table 8). Gemifloxacin also has the highest free drug C_{max}/MIC_{90} ratio and is the only quinolone to achieve the target C_{max}/MIC_{90} ratio of greater than 10.

Table 8: Comparative Free Drug Pharmacokinetic/Pharmacodynamic Parameters for *S. pneumoniae*

Antimicrobial (dose)	24 h AUC^a/MIC_{90}^b	24 h C_{max}^a/MIC_{90}^b
Gemifloxacin (320 mg)	2.9-3.8/0.03 = 97-127	0.56-0.72/0.03 = 18.7-24
Moxifloxacin (400 mg)	24.0/0.25 = 96	2.3/0.25 = 9.2
Gatifloxacin (400 mg)	41.0/0.5 = 82	3.4/0.5 = 6.8
Levofloxacin (500 mg)	29.5-36.1/1.0 = 30-36	3.5-4.3/1.0 = 3.5-4.3

^a Data from product prescribing information for moxifloxacin, gatifloxacin, and levofloxacin. Data from NDA 21-158 Item 6 for gemifloxacin 24 h AUC (Section B.6, Figure 8) and C_{max} (Section B.5.2, Table 6).

^b MIC_{90} s from recent U.S. surveillance study

Examination of these PK/PD parameters predicts that gemifloxacin has the potential for good clinical efficacy, with a low potential for resistance generation.

In addition, more recently, an additional marker of relevance to respiratory infection has been elucidated (Craig, personal communication), the selective concentration of drug at the target respiratory site, the epithelial lining fluid (ELF). At a plasma concentration of 1.4 $\mu\text{g/mL}$ (+/- 0.44 2SD) the concentration in ELF is 2.69 $\mu\text{g/mL}$ (+/-1.96SD), giving an ELF/plasma ratio of 1.99.

The proposed gemifloxacin MIC breakpoints for respiratory pathogens are shown in Table 9.

Table 9: Proposed MIC Breakpoints

	MIC (µg/mL)		
	Susceptible	Intermediate	Resistant
Gemifloxacin	≤0.25	0.5	≥1.0

The choice of breakpoint was based upon PK/PD parameters described above, with the critical value for the AUC₂₄/MIC₉₀ ratio for fluoroquinolones of 25-30. Based on a total AUC₂₄ in man of 8.4 µg.h/mL an MIC₉₀ of 0.25 µg/mL for gemifloxacin yields a ratio of 34. This breakpoint is supported by experimental *in vivo* infections studies, gemifloxacin demonstrated significant efficacy against all *S. pneumoniae* tested with MICs of 0.25 µg/mL.

Two study subjects in the clinical development program were noted to have clinical isolates of *S. pneumoniae* that demonstrated gemifloxacin sensitivities at or above the sponsor's proposed breakpoint of 0.25 µg/mL and 0.5 µg/mL. Both study subjects participated in AECB trials, and both were considered to have had a successful clinical outcome while receiving gemifloxacin.

6.3.1 Gemifloxacin Activity in the Face of Rising Antibiotic Resistance

The favorable characteristics of gemifloxacin mentioned above have a number of positive implications for its clinical use. One consequence is that gemifloxacin can be given for shorter courses of therapy relative to other antimicrobial agents. This is more convenient for the patient and has the potential to increase compliance. Furthermore, decreased antibiotic use, in conjunction with shorter treatment regimens, may reduce the development of antibiotic resistance, as described more fully in Section 6.3.3.

Also of great impact is the ability of gemifloxacin to treat antibiotic-resistant *S. pneumoniae* infections, including those caused by penicillin-, macrolide-, and cephalosporin-resistant strains. Most importantly, gemifloxacin also shows activity against *S. pneumoniae* strains resistant to other quinolones, such as levofloxacin, moxifloxacin, and gatifloxacin (Forrest et al. 1993; Craig 1998; Preston et al. 1998; Woodnutt 2000; Dagan et al. 2001). The activity of gemifloxacin against drug-resistant bacteria has been demonstrated *in vitro*, *in vivo*, and in clinical trials, where effective bacteriologic and clinical cures were demonstrated in patients with various resistance patterns, including patients with quinolone-resistant *S. pneumoniae* isolates.

6.3.2 *In Vitro* Data on Gemifloxacin Activity Against Resistant *S. Pneumoniae*

Several surveillance studies have demonstrated that gemifloxacin has the lowest MICs against *S. pneumoniae* non-susceptible to penicillin (Table 10) and macrolides (Table 11).

Table 10: *In Vitro* Activity of Gemifloxacin and Comparators Against Penicillin Non-Susceptible Isolates of *S. Pneumoniae*

# of Isolates	Penicillin MIC (µg/mL)	MIC ₉₀ (µg/mL)				
		Gemifloxacin	Ciprofloxacin	Levofloxacin	Gatifloxacin	Moxifloxacin
1,050	0.12-1	0.047	NT	1	NT	NT
75	0.12-1	0.06	NT	1	0.5	0.125
67	0.12-1	0.03	2	1	0.5	0.25
1,016	≥2	0.047	NT	1	NT	NT
143	≥2	0.015	1	1	0.25	0.125

NT = not tested

Table 11: *In Vitro* Activity of Gemifloxacin and Comparators Against Isolates of Macrolide Resistant *S. Pneumoniae*

# of Isolates	Macrolide Resistance Criteria	MIC ₉₀ (µg/mL)			
		Gemifloxacin	Ciprofloxacin	Levofloxacin	Gatifloxacin
1,505	Erythromycin MIC ≥1 µg/mL	0.047	NT	1	NT
115	Clarithromycin MIC ≥1 µg/mL	0.06	2	2	0.25

NT = not tested

6.3.2.1 *In Vitro* Data on *S. Pneumoniae* Resistant to Quinolones

Decreased susceptibility of *S. pneumoniae* to fluoroquinolones primarily occurs through three mechanisms: mutations in the *gyrA* subunit of DNA gyrase, mutations in the *parC* subunit of topoisomerase IV, and/or active efflux of the drug from the cell (Janoir et al. 1996; Tankovic et al. 1996; Drlica & Zhao 1997; Jorgensen et al. 1999). Quinolone resistance in *S. pneumoniae* can be defined either phenotypically, as determined by an elevated MIC, or mechanistically, using molecular techniques to define sequence changes in the relevant genes. Studies on the gemifloxacin susceptibility of quinolone-resistant *S. pneumoniae*, as defined by both of these criteria, are described below.

6.3.2.1.1 Phenotypic Quinolone Resistance

For ciprofloxacin, non-susceptible *S. pneumoniae* are defined as organisms with an MIC ≥ 2 $\mu\text{g/mL}$, while resistant organisms have a ciprofloxacin MIC ≥ 4 $\mu\text{g/mL}$. For levofloxacin, the non-susceptible and resistant breakpoints are ≥ 4 $\mu\text{g/mL}$ and ≥ 8 $\mu\text{g/mL}$, respectively.

In a study of 167 ciprofloxacin-resistant *S. pneumoniae* isolates from Canada, the MIC₉₀ for gemifloxacin was 0.5 $\mu\text{g/mL}$, at least 8-fold lower and as much as 64-fold lower than that of any of the other quinolones tested (Table 12). In a separate Canadian study, 90 isolates with reduced susceptibility to ciprofloxacin were investigated. The MIC₉₀ for gemifloxacin was 0.25 $\mu\text{g/mL}$ compared with 2, 4, 16, and 32 $\mu\text{g/mL}$ for moxifloxacin, gatifloxacin, levofloxacin, and ciprofloxacin, respectively. Again, the MIC₉₀ for gemifloxacin was at least 8-fold lower and as much as 128-fold lower than that of the other quinolones tested (Table 12).

Table 12: *In Vitro* Activity of Gemifloxacin and Comparators Against Isolates of Ciprofloxacin Non-Susceptible *S. Pneumoniae*

# of Isolates	Ciprofloxacin MIC ($\mu\text{g/mL}$)	MIC ₉₀ ($\mu\text{g/mL}$)				
		Gemifloxacin	Ciprofloxacin	Levofloxacin	Gatifloxacin	Moxifloxacin
167	≥ 4	0.5	32	16	4	4
90	≥ 2	0.25	32	16	4	2

Table 13 shows the results of two additional studies of *S. pneumoniae* isolates with levofloxacin MICs ≥ 8 $\mu\text{g/mL}$ as tested against levofloxacin, gatifloxacin, and gemifloxacin. The gemifloxacin MIC₉₀ was 1 $\mu\text{g/mL}$ and 0.5 $\mu\text{g/mL}$, 4- to 16-fold lower than comparator quinolones.

Table 13: *In Vitro* Activity of Gemifloxacin and Comparators Against Isolates of Levofloxacin Non-Susceptible *S. Pneumoniae*

# of Isolates	Levofloxacin MIC ($\mu\text{g/mL}$)	MIC ₉₀ ($\mu\text{g/mL}$)			
		Gemifloxacin	Levofloxacin	Gatifloxacin	Moxifloxacin
57	≥ 8	1	>16	8	NT
32	≥ 4	0.5	8	4	2

NT = not tested

From January 2000 through February 2002, a large surveillance study was conducted on a cross sectional population in the U.S. This prospective study analyzed the *in vitro* activity of gemifloxacin against *S. pneumoniae* presumed to have both first- and second-step mutations, using a levofloxacin marker (MICs >2 µg/mL). 7,553 isolates of *S. pneumoniae* were tested from 124 investigational centers; only one clinical isolate was taken per patient from a clearly identified respiratory, blood, or body fluid. 0.2% of isolates were intermediate, and 0.8% were resistant; 0.9% were non-susceptible to levofloxacin (MIC ≥3 µg/mL) (Table 14). Gemifloxacin had the lowest MIC₉₀ (1 µg/mL) compared to moxifloxacin (12 µg/mL), gatifloxacin, and levofloxacin, (both >32 µg/mL).

Table 14: Phase II Results: *In Vitro* Activity (MIC µg/mL) of Gemifloxacin and Comparative Agents Against 77 *S. pneumoniae* Isolates Non-Susceptible to Levofloxacin (MIC >2 µg/mL)

Drug	%Sus	%Int	%Res	MIC ₅₀	MIC ₉₀	Range
Gemifloxacin ^a	54.5	28.6	16.9	0.25	1	0.047 / 3
Gatifloxacin	23.4	11.7	64.9	4	>32	0.125 / >32
Levofloxacin	0.0	20.8	79.2	>32	>32	3 / >32
Moxifloxacin	27.3	16.9	55.8	3	12	0.047 / >32

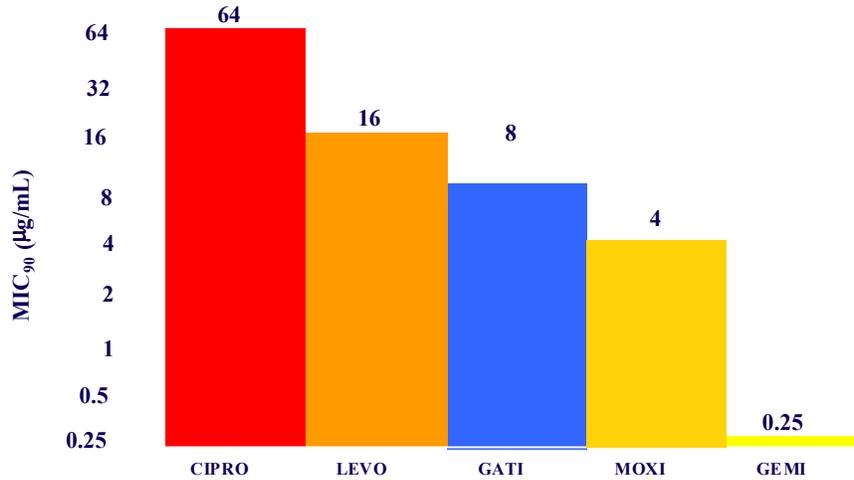
^a Gemifloxacin susceptible *S. pneumoniae* is defined as a MIC ≤0.25 µg/mL; intermediate = 0.5 µg/mL; and resistant ≥1 µg/mL.

6.3.2.1.2 Molecularly Defined Quinolone Resistance

Recent studies have demonstrated that *gyrA/parC* double mutants are resistant to most fluoroquinolones in clinical use. The data provided within NDA 21-376 (Item 3A, attachment 2) demonstrate that 98% of such isolates were resistant to ciprofloxacin (using a resistant breakpoint of ≥4 µg/mL) and ofloxacin; 95% were resistant to levofloxacin, 82% to gatifloxacin, and 25% to moxifloxacin. On the other hand, at the proposed breakpoint of ≤0.25 µg/mL, gemifloxacin maintains activity against 41 of 44 *S. pneumoniae* isolates demonstrating second step mutations in the target binding sites. The gemifloxacin MIC₉₀ against these double mutants was 16-fold lower than that of moxifloxacin, 32-fold lower than that of gatifloxacin, and 64-fold lower than that of levofloxacin (Figure 3).

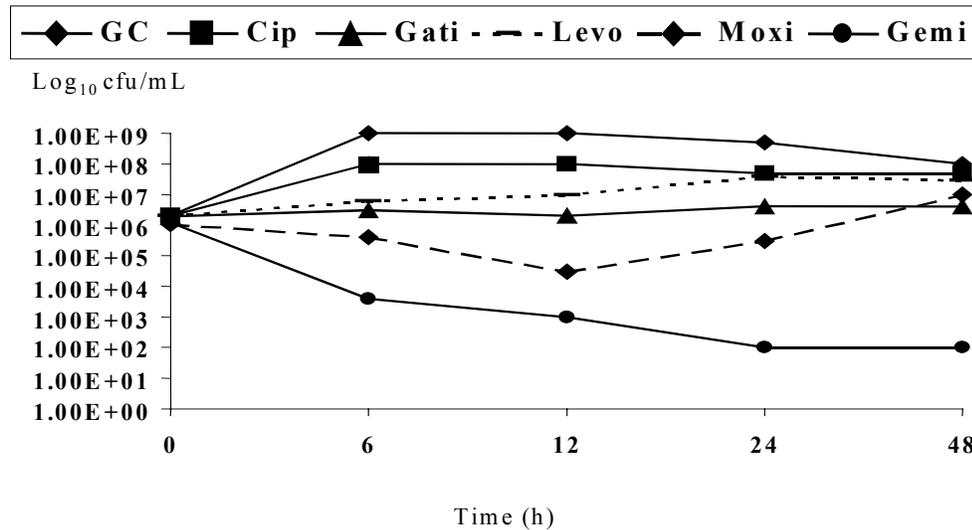
Two mutations in the quinolone resistance-determining regions (QRDR) are required for significant resistance to gemifloxacin to arise, in contrast to levofloxacin, for which resistance can arise from a single mutation.

Figure 3: Activity of Gemifloxacin and Comparator Quinolones Against *S. pneumoniae* Demonstrating Second Step Mutations in the QRDR



Zhanel et al. (2002) used an *in vitro* pharmacodynamic model to examine bacterial killing by gemifloxacin, moxifloxacin, gatifloxacin, levofloxacin, and ciprofloxacin against a variety of first and second step quinolone-resistant *S pneumoniae* simulating free fluoroquinolone (protein unbound) C_{max} and AUCs achieved in human serum after standard oral doses. The data suggest that ciprofloxacin produces no inhibition in growth against low or high level ciprofloxacin-resistant *S. pneumoniae*, while gatifloxacin, levofloxacin, and moxifloxacin were bactericidal against low-level resistant strains but produced little to no inhibition of high-level resistant strains (Figure 4). Gemifloxacin was bactericidal against both low and high level resistant strains and was the only fluoroquinolone to eradicate the high-level ciprofloxacin-resistant *S. pneumoniae* from the model and maintain this effect over 48 hours. Gemifloxacin was bactericidal against both first and second step resistant strains.

Figure 4: Fluoroquinolone Killing of a Quinolone-Resistant *S. Pneumoniae* Isolate (17012) Simulating Free AUC₂₄/MIC Ratios



Strain	Cip	Levo	Gati	Moxi	Gemi	<i>ParC</i> Change	<i>GyrA</i> Change	Efflux
17012	16	8	4	2	0.12	Yes	Yes	No

6.3.2.2 *In Vivo* Models of *S. Pneumoniae* Respiratory Tract Infection

The efficacy of gemifloxacin has also been examined in experimental rat respiratory infections caused by strains of *S pneumoniae* with reduced susceptibility to quinolones (Table 15). These strains had gemifloxacin MICs ≥ 0.125 $\mu\text{g}/\text{mL}$ and were highly resistant to ciprofloxacin and levofloxacin; 6 of them were genetically-defined second step mutants. In these studies, gemifloxacin exhibited excellent efficacy against all strains of *S. pneumoniae* with gemifloxacin MICs of 0.125 - 0.25 $\mu\text{g}/\text{mL}$, and good efficacy against 2 of 5 strains of *S. pneumoniae* with MICs of 0.5 $\mu\text{g}/\text{mL}$. These data confirm the effectiveness of gemifloxacin for the treatment of infections caused by strains of *S pneumoniae* resistant to other fluoroquinolones. Importantly, gemifloxacin showed improved efficacy relative to levofloxacin against all ciprofloxacin-resistant *S. pneumoniae*, including isolates with second step mutations.

Table 15: Efficacy of Gemifloxacin against Respiratory Tract Infections in the Rat Caused by *S. Pneumoniae* with Differing *In Vitro* Susceptibilities

<i>S. pneumoniae</i> Strain	Resistance Profile	MIC (µg/mL)		CFU/Lungs		
		Gemi	Levo	NTC	Gemi	Levo
305313	CIP-R	0.125	1	7.9±0.4	3.3±1.3 ^{a,b}	5.7 ±1.3 ^a
622286	CIP-R/MAC-R	0.125	4	6.4±1.3	2.5±1.1 ^{a,b}	5.1 ± 1.3
PT9424123	CIP-R	0.25	16	8.1±0.8	4.4±0.7 ^{a,b}	6.8 ± 0.6 ^a
402123 ⁺	CIP-R	0.25	8	8.3±0.8	5.7±0.9 ^{a,b}	7.3 ± 1.2
509063 ⁺	CIP-R	0.25	8	6.2±1.6	3.5±1.1 ^{a,b}	6.2 ± 0.7
214152 ⁺	CIP-R	0.5	16	6.6 ± 1.6	3.8 ± 1.4 ^a	5.0 ± 1.4
TPS 3 ⁺	CIP-R	0.5	16	6.7±0.4	5.5±1.8	5.9 ± 1.3
TPS 5 ⁺	CIP-R	0.5	32	6.2±0.5	4.5±1.2 ^{a,b}	5.7 ± 0.5
703316 ⁺	CIP-R	0.5	>16	6.6±0.4	6.2±0.9	6.5 ± 0.3
42064	CIP-R	0.5	16	6.7±0.3	5.4±1.9	5.2 ± 1.1

CIP-R = ciprofloxacin resistant; MAC-R = macrolide resistant; CFU = colony forming units

^a Significant difference compared with untreated controls (p≤0.01)

^b Significant difference compared with levofloxacin (p<0.01)

⁺ Genetically-defined second step mutants

The efficacy of gemifloxacin in comparison with moxifloxacin and gatifloxacin in experimental models of respiratory tract infection (RTI) caused by *S. pneumoniae* was also examined. The susceptibility of the strains tested to the agents is shown in Table 16.

Table 16: MICs of Gemifloxacin, Moxifloxacin, and Gatifloxacin against *S. pneumoniae* Isolates used in the Rat RTI Model

<i>S. pneumoniae</i> Strain	MIC (µg/mL)		
	Gemifloxacin	Moxifloxacin	Gatifloxacin
404053	≤0.03	0.06	0.125
406081	≤0.03	0.125	0.25
205118	≤0.03	0.25	1.0
305313	0.125	2.0	4.0
509063 ⁺	0.25	2.0	4.0
PT9424123	0.25	2.0	4.0
622286	0.125	1.0	1.0
402123 ⁺	0.25	2.0	4.0

⁺ Genetically-defined second step mutants

With the exception of gatifloxacin against *S. pneumoniae* 509063, all therapies were significantly effective compared with untreated animals ($p \leq 0.01$) (Table 17). Gemifloxacin was highly effective against all strains tested and showed significant improvements ($p \leq 0.05$) in effect against some strains compared with moxifloxacin (*S. pneumoniae* 205118 and 622286) and gatifloxacin (*S. pneumoniae* 205118 and 509063). Neither moxifloxacin nor gatifloxacin showed better efficacy than gemifloxacin against any strain.

Table 17: Efficacy of Gemifloxacin, Moxifloxacin, and Gatifloxacin against *S. pneumoniae* in the Rat RTI Model

<i>S. pneumoniae</i> Strain	Log ₁₀ CFU/lungs			
	Gemifloxacin	Moxifloxacin	Gatifloxacin	Non-treated Controls
404053	≤1.7	≤1.7	≤1.7	6.5 ± 1.5
406081	≤1.7	≤1.7	≤1.7	6.8 ± 1.0
205118	1.9 ± 0.6*, **	2.9 ± 1.6	3.7 ± 1.1	6.3 ± 1.1
305313	4.0 ± 0.8	3.5 ± 1.4	4.1 ± 1.4	6.1 ± 1.5
509063 ⁺	3.8 ± 1.6*	4.6 ± 1.3	6.1 ± 1.2 ^c	7.0 ± 0.4
PT 9424123	3.1 ± 0.7	3.6 ± 1.9	4.0 ± 1.4	6.8 ± 1.4
622286	2.6 ± 1.2**	4.6 ± 2.0	3.6 ± 2.3	7.4 ± 1.4
402123 ⁺	3.6 ± 1.1	3.9 ± 1.3	3.1 ± 1.1	6.1 ± 2.2

* Significantly different compared with gatifloxacin $p < 0.05$

** Significantly different to moxifloxacin $p < 0.05$

^c Not significantly different to non-treated controls ($p > 0.05$)

⁺ Genetically-defined second step mutants

In summary, gemifloxacin had an excellent effect against all strains of *S. pneumoniae* tested and importantly afforded good protection against ciprofloxacin-resistant strains of *S. pneumoniae*, including isolates demonstrating second step mutations in the QRDR. Overall, gemifloxacin was the most effective agent tested in experimental RTI caused by strains of *S. pneumoniae* having varying susceptibility to standard antimicrobial agents. The excellent effect obtained confirms the impressive *in vitro* activity of gemifloxacin against this organism and indicates a high potential benefit for the use of gemifloxacin in the treatment of RTIs caused by *S. pneumoniae*.

6.3.3 Gemifloxacin and Likelihood of Resistance Development

As described above, resistance to gemifloxacin can arise either through mutations in DNA gyrase and topoisomerase IV, or through altered efflux. Recent data from an *in vitro* pharmacokinetic

model have found that efflux has little effect on the activity of gemifloxacin, suggesting that efflux mechanisms of quinolone-resistance may be significantly down-regulated *in vivo* (Study No. SB-265805/RSD-1010XM/2).

The reported spontaneous resistance rates for marketed respiratory quinolones in *S. pneumoniae* is high, 1 in 10^7 bacteria. This corresponds to the frequency of a single step mutation. The *S. pneumoniae* bacterial load in pneumonia has been assessed in post mortem specimens at 10^{12} - 10^{14} CFU (Frisch 1942), such that first step mutants would be anticipated to arise in each pneumonia patient treated with a current respiratory quinolone. These results are consistent with the seemingly rapid emergence of quinolone non-susceptible *S. pneumoniae*. Thus, not surprisingly, quinolone-resistant strains of *S. pneumoniae* have been described in the U.S., Canada, and Europe (Chen et al. 1999; Jones et al. 2000; Empey et al. 2001; Zheng et al. 2001; Anderson et al. 2002; Davidson et al. 2002; Ferraro 2002; Ross et al. 2002).

Historically, this situation is analogous to previous experiences with tuberculosis therapy. Drug resistance in *Mycobacterium tuberculosis* is also mediated by chromosomal point mutations, at a similar frequency. A rapid emergence of resistance was consequently observed, along with the need for multi-drug therapy. Gemifloxacin, a dual targeting quinolone, is analogous to combination therapy. Double mutations are a rare genetic event, occurring at a frequency of 10^{-14} for fluoroquinolones in *S. pneumoniae* (Blondeau et al. 2001). Thus, gemifloxacin would be anticipated to limit the incidence of fluoroquinolone resistance. This is supported by gemifloxacin's low mutant prevention concentrations (MPCs); among the quinolones tested, the rank order of potency (based on MPC₉₀ values) was gemifloxacin > moxifloxacin > gatifloxacin > levofloxacin.

Because gemifloxacin is the only quinolone to retain anti-pneumococcal activity in the face of quinolone resistance, its importance for the treatment of respiratory infection is likely to grow as the incidence of bacterial drug resistance increases. The concern over quinolone resistance is clinically relevant. Bacteria with levofloxacin resistance have been described and resistant mutants have been documented to cause disease in patients. In two studies, resistant strains were associated with clinical and microbiologic failure when patients were treated empirically with levofloxacin for respiratory tract infections. In these studies, all collected baseline isolates were susceptible to gemifloxacin; isolates from 5 of the 8 patients remained susceptible to gemifloxacin following emergence of levofloxacin resistance. The last isolate, collected from the single patient who died, was gemifloxacin susceptible. Additionally, all of the levofloxacin-resistant organisms were either resistant or intermediate susceptibility to moxifloxacin and gatifloxacin (Davidson 2002; Low 2002).

7. REVIEW OF GEMIFLOXACIN EFFICACY IN ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS

7.1 Background and Rationale

Chronic bronchitis is a major health problem that is associated with significant morbidity and mortality. It is estimated that chronic bronchitis affects up to 13 million individuals or approximately 4 to 6% of adults in the U.S. (American Thoracic Society 1995; Sethi 1999). Prevalence is higher in men than women; however, the prevalence in women is increasing in parallel with increased rates of smoking which is a major factor associated with disease development (Sethi 1999).

Chronic bronchitis is defined in clinical terms as a chronic productive cough with sputum production for at least 2 years and for most days in a consecutive 3-month period (American Thoracic Society 1995). Patients with chronic bronchitis are prone to frequent exacerbations, characterized by increased cough, increased sputum volume and purulence, and respiratory distress. Longitudinal studies have estimated that one to four exacerbations occur each year in patients with chronic bronchitis, and such exacerbations are estimated to account for approximately 12 million physician visits per year in the U.S. (Bilas 1990; Ball 1995). Although AECB is not always regarded as a major illness, as many as 20 to 60% of patients admitted to an intensive care unit with this diagnosis will require mechanical ventilation, with an associated mortality rate of 10 to 30% (Seneff et al. 1995).

The pathogens commonly associated with AECB include *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*, and these are estimated to account for approximately 70% of all episodes of AECB (Ball 1995). Other bacteria such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* are less frequently recovered from bronchial secretions of patients with AECB. The atypical pathogens, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, are postulated to be pathogens in AECB at low frequency (Sethi 1999).

Antibiotic therapy has been shown to be important in reducing the course of illness in patients with AECB and is considered by most physicians to represent the appropriate standard of care (Ball 1995). Since a microbiological diagnosis is often difficult to establish and diagnosis is usually made based on symptoms and clinical assessment, empirical antibiotic therapy is normal practice in the treatment of this condition.

Although β -lactam antibiotics are commonly prescribed agents for the treatment of lower respiratory tract infections, including AECB, clinical utility is often limited in the treatment of infections due to *Haemophilus influenzae* and *Moraxella catarrhalis* because of the increasing incidence worldwide of β -lactamase-producing and macrolide-resistant strains. The increasing incidence of *Streptococcus pneumoniae* resistant to penicillin and macrolides has further

increased the concern regarding the efficacy of these agents in the management of AECB (Doern 1995; Butler et al. 1996; Doern et al. 1996; Cunha and Shea 1998). Therefore, new agents that are well tolerated and efficacious in the treatment of infections caused by these organisms are necessary. The newer quinolones, particularly those with enhanced Gram-negative activity (since these pathogens are predominant in AECB), represent attractive alternatives to other antibiotic classes due to their enhanced antimicrobial potency and high levels in respiratory secretions. Gemifloxacin - the newest quinolone - represents an attractive alternative to other antibiotics classically used to treat patients with AECB, especially those with severe disease, because of its convenient and efficacious oral dosing with no requirement for an intravenous to oral switch, keeping patients, in particular the elderly, mobile.

7.2 Overview of Gemifloxacin Clinical Program in AECB

The clinical program to evaluate the efficacy of gemifloxacin (320 mg PO for 5 days) in the treatment of AECB consisted of 3 double-blind, randomized, actively-controlled clinical studies (Studies 068, 070, and 212), 2 supportive studies (Studies 069 and 207) and 6 other clinical studies (Studies 001, 008, 061, 105, 112, and 139) (Table 18). The design of all gemifloxacin AECB studies followed the recommendations of Infectious Diseases Society of America and the FDA (Chow et al. 1992).

Table 18: Acute Exacerbation of Chronic Bronchitis: Principal, Supportive, and Other Studies

Study	Study Title	Treatment Regimen	Duration	N	Geographic Region
Principal Controlled Studies					
068	SB-265805/RSD-100WPL/1 SB-265805/068. A Randomized, Double-Blind, Double-Dummy, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Oral Gemifloxacin 320 mg Once Daily for Five Days Versus Oral Clarithromycin 500 mg Twice Daily for Seven Days for the Treatment of Acute Exacerbation of Chronic Bronchitis	gemifloxacin 320 mg PO	5 days	340	Europe, U.S., Canada
		clarithromycin 500 mg bid	7 days	351	
070	SB-265805/RSD-100ZW7/1 SB-265805/070. A Randomized, Double-Blind, Double-Dummy, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Oral Gemifloxacin 320 mg Once Daily for 5 Days Versus Oral Amoxicillin/Clavulanate 500/125 mg Three Times Daily for Seven Days for the Treatment of Acute Exacerbation of Chronic Bronchitis	gemifloxacin 320 mg PO	5 days	304	Europe
		amoxicillin/clavulanate 500/125 mg tid	7 days	296	
212	SB-265805/RSD-101947/1. SB-265805/212. A Randomized, Double-Blind, Double-Dummy, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Oral Gemifloxacin (Factive™) 320 mg Once Daily for 5 Days Versus Oral Levofloxacin 500 mg Once Daily for 7 Days for the Treatment of Acute Exacerbation of Chronic Bronchitis	gemifloxacin 320 mg PO	5 days	182	Europe, U.S
		levofloxacin 500 mg PO	7 days	179	
Supportive Studies					
069	SB-265805/RSD-100ZFX/1 SB-265805/069. A Randomized, Double-Blind, Double-Dummy, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Oral Gemifloxacin 320 mg Once Daily for Five Days Versus Oral Trovafloxacin 200 mg Once Daily for Five Days for the Treatment of Acute Exacerbation of Chronic Bronchitis	gemifloxacin 320 mg PO	5 days	303	Europe
		trovafloxacin 200 mg PO	5 days	314	
207	SB-265805/RSD-101794/1. SB-265805/207. A Randomized, Open-Label, Controlled, Multicenter Study to Compare the Efficacy, Safety and Tolerability of Oral Gemifloxacin versus Parenteral Ceftriaxone Followed by Oral Cefuroxime Axetil in the Treatment of Hospitalised Adult Patients with Acute Exacerbation of Chronic Bronchitis	gemifloxacin 320 mg PO	5 days	138	Europe, Mexico, South Africa
		ceftriaxone 1 g IV PO / cefuroxime 500 mg bid	1-3days/ 7days	136	

Study	Study Title	Treatment Regimen	Duration	N	Geographic Region
Other Studies					
008	SB-265805/RSD-100WPF/1 SB-265805/008. A Randomized, Double-Blind, Double-Dummy, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Oral Gemifloxacin 320 mg Once Daily for Seven Days Versus Oral Levofloxacin 500 mg Once Daily for Seven Days for the Treatment of Acute Exacerbation of Chronic Bronchitis	gemifloxacin 320 mg PO	7 days	280	U.S., Canada
		levofloxacin 500 mg PO	7 days	281	
061*	SB-265805/RSD-100ZW4/1 SB-265805/061. An Open, Non-Comparative, Multicenter Study to Assess the Efficacy and Safety of Oral Gemifloxacin 320 mg Once Daily for Seven Days for the Treatment of Lower Respiratory Infections in Adults	gemifloxacin 320 mg PO	7 days	261	World-wide/ except N. America
001 (phase II)	SB-265805/RSD-100V63/2. SB-265805/001. A Double-Blind, Multicentre, Parallel Group, Dose Ranging Study to Compare the Efficacy and Safety of Oral SB-265805 at Doses of 80 mg, 160 mg or 320 mg (Equivalent to 100 mg, 200 mg or 400 mg of Mesylate Salt) Once Daily Versus Oral Ofloxacin 400 mg Twice Daily for 10 Days for the Treatment of Acute Bacterial Exacerbations of Chronic Bronchitis	gemifloxacin 80 mg PO	10 days	67	Europe, N. America
		gemifloxacin 160 mg PO	10 days	67	
		gemifloxacin 320 mg PO	10 days	64	
		ofloxacin 400 mg bid	10 days	69	
105	SB-265805/RSD-10170T/3. SB-265805/105. An Experimental Study to Investigate Pharmacokinetic and Pharmacodynamic Properties of 320 mg Oral FACTIVE (Gemifloxacin) Once Daily for 5 Days versus 500 mg Oral Clarithromycin Twice Daily for 7 Days in Patients with Acute Exacerbations of Chronic Bronchitis at Risk of Early Recurrence	gemifloxacin 320 mg PO	5 days	83	Europe, U.S.
		clarithromycin 500 mg bid	7 days	80	
112	SB-265805/RSD-101FK9/1. SB-265805/112. A Randomized, Double-Blind, Double-Dummy, Multicenter, Parallel Group Study to Assess the Effectiveness and Health Economic Impact of Oral Factive™ (Gemifloxacin), 320 mg Once Daily for 5 Days Versus Oral Clarithromycin 500 mg Twice Daily for 7 Days for the Treatment of Acute Exacerbation of Chronic Bronchitis	gemifloxacin 320 mg PO	5 days	908	Europe, Australia, Brazil, Canada, Mexico, U.S.
		clarithromycin 500 mg bid	7 days	897	
139	SB-265805/RSD-101568/1. SB-265805/139. A Health Economics Study to Assess the Cost Effectiveness of Using Oral Gemifloxacin 320 mg Once Daily for 5 Days Versus Oral Clarithromycin 500 mg Twice Daily for 7 Days for the Treatment of Acute Exacerbations of Chronic Bronchitis	gemifloxacin 320 mg PO	5 days	214	U.S., Canada
		clarithromycin 500 mg bid	7 days	224	

N = number of patients randomized to treatment

*Study 061 was conducted in patients with CAP or AECB. Only those patients with AECB are summarized in this section

7.3 Demography and Patient Characteristics

In the principal gemifloxacin studies in AECB, a total of 826 patients received treatment with gemifloxacin 320 mg PO once daily and 822 patients received treatment with active comparator (4 patients who were randomized in the active comparator group were not treated). The incidence of patient withdrawals was similar between the two treatment groups in Studies 068 and 070. In Study 212 there were significantly fewer patients withdrawn from the study (i.e., withdrawn for any reason) in the gemifloxacin treatment group versus the levofloxacin treatment group [gemifloxacin: 7/182 (3.8%) patients, levofloxacin: 18/178 (10.1%) patients; (Fisher's Exact Test; P-value = 0.02)].

In the controlled AECB studies treatment groups were generally well matched with respect to demographic and baseline characteristics. No major differences between the clinical per protocol (PP) and intent to treat (ITT) populations were noted.

The characteristics of the two study populations were typical of patients with AECB. Patients were generally elderly and had suffered from chronic bronchitis for an average of 12 to 14 years. The majority of patients in both studies were classified as having Stage 2 AECB, with only a small proportion of patients meeting the definition of severe Stage 3 AECB [based on published severity categories (Ball and Make 1998; Table 19)]. Consistent with this classification, most patients had between 1 to 4 exacerbations treated with antibacterials in the last year. It should be noted that stage 2 is consistent with the Anthonisen type I classification, which is also characterized by increase in dyspnea, cough, and sputum purulence (Anthonisen et al 1987). Anthonisen type I patients have a demonstrable treatment benefit from antibiotic therapy.

Table 19: AECB Severity Criteria (Ball and Make 1998)

Severity	Background Status	Exacerbation Definition
Stage 1	Simple mucus hypersecretion	Patients without a history of chronic bronchitis as defined in the protocol.
Stage 2	Simple chronic bronchitis (2-3 year history of cough and sputum for 2-3 months/year)	Patients had a history of chronic bronchitis as defined in the protocol and had an increase in: (a) dyspnea, (b) volume of purulent sputum.
Stage 3	Complicated chronic bronchitis	Patients met the Stage 2 criteria plus the following: (a)>4 episodes of AECB in previous year, (b) co-morbidity, (c) 10 year history of AECB

Approximately one third of patients in each of the treatment groups in Study 070 and 212 had a reduction in FEV1 measurement to less than 50% of predicted value indicating severe airflow

limitation (FEV1 was not measured in Study 068) (Table 20). The bacterial pathogens isolated were also typical of those seen in patients with AEBC and were evenly distributed between the gemifloxacin and comparator treated patients (Table 21).

Table 20: Demographic and Baseline Characteristics: AECB Principal Studies 068, 070, and 212 (Clinical PP)

	Study 068		Study 070		Study 212			
	Gemifloxacin 320 mg PO	Clarithromycin 500 mg bid	Gemifloxacin 320 mg PO	Amoxicillin/ Clavulanate 500/125 mg tid	Gemifloxacin 320 mg PO	Levofloxacin 500 mg PO		
Population	N=278		N=264		N=152		N=148	
Gender: n (%)								
Male	139 (50.0)	148 (52.3)	141 (53.4)	157 (59.0)	76 (50.0)	80 (54.1)		
Female	139 (50.0)	135 (47.7)	123 (46.6)	109 (41.0)	76 (50.0)	68 (45.9)		
Age								
Mean (SD)	59.6 (11.7)	58.5 (11.4)	64.1 (11.7)	63.8 (12.2)	60.6 (11.1)	63.5 (10.6)		
Range	37 - 88	39 - 88	40 - 92	41 - 97	34 - 84	39 - 89		
Race: n (%)								
White	235 (84.5)	248 (87.6)	262 (99.2)	263 (98.9)	145 (95.4)	144 (97.3)		
Black	15 (5.4)	13 (4.6)	0	1 (0.4)	1 (0.7)	1 (0.7)		
Oriental	2 (0.7)	2 (0.7)	2 (0.8)	1 (0.4)	3 (2.0)	1 (0.7)		
Other	26 (9.4)	20 (7.1)	0	1 (0.4)	3 (2.0)	2 (1.4)		
Duration of chronic bronchitis (years)								
Mean (SD)	12.6 (12.1)	12.0 (11.6)	13.5 (11.8)	13.5 (10.6)	12.3 (10.9)	12.9 (11.9)		
Range	2.0 - 65.1	2.0 - 66.2	1.9 - 78.8	2.0 - 58.8	2 - 56	2 - 61		
Exacerbations treated with antibacterials in last year, n (%)								
0	52 (18.7)	54 (19.1)	17 (6.4)	24 (9.0)	20 (13.2)	18 (12.2)		
1-4	195 (70.1)	199 (70.3)	193 (73.1)	203 (76.3)	121 (79.6)	112 (75.7)		
>4	29 (10.4)	30 (10.6)	53 (20.1)	39 (14.7)	11 (7.2)	18 (12.2)		
Unknown	2 (0.7)	0	1 (0.4)	0	0	0		
Smoking pack years, n (%)								
0	59 (21.2)	64 (22.6)	88 (33.3)	86 (32.3)	37 (24.3)	34 (23.0)		
>0-30	99 (35.6)	98 (34.6)	96 (36.4)	103 (38.7)	59 (38.8)	45 (30.4)		
>30	119 (42.8)	120 (42.4)	77 (29.2)	73 (27.4)	56 (36.8)	69 (46.6)		
Unknown	1 (0.4)	1 (0.4)	3 (1.1)	4 (1.5)	0	0		
Severity of AECB, n (%)								
Stage 2	270 (97.1)	272 (96.1)	238 (90.2)	250 (94.0)	146 (96.1)	140 (94.6)		
Stage 3	8 (2.9)	11 (3.9)	25 (9.5)	16 (6.0)	6 (3.9)	8 (5.4)		

Table 21: Number (%) of Patients with Key Pathogens Associated with AECB at Screening: Principal AECB Studies

Bacteriology Population	Study 068		Study 070		Study 212			
	Gemifloxacin 320 mg PO	Clarithromycin 500 mg bid	Gemifloxacin 320 mg PO	Amoxicillin/ Clavulanate 500/125 mg tid	Gemifloxacin 320 mg PO	Levofloxacin 500 mg PO		
PP Follow-Up	N=40		N=44		N=37		N=49	
<i>H. influenzae</i>	14 (35.0)	14 (31.8)	12 (27.3)	6 (13.6)	7 (18.9)	11 (22.4)		
<i>M. catarrhalis</i>	4 (10.0)	6 (13.6)	14 (31.8)	13 (29.5)	6 (16.2)	14 (28.6)		
<i>S. pneumoniae</i>	8 (20.0)	4 (9.1)	7 (15.9)	9 (20.5)	4 (10.8)	5 (10.2)		
<i>H. parainfluenzae</i>	5 (12.5)	4 (9.1)	2 (4.5)	0	7 (18.9)	6 (12.2)		
<i>S. aureus</i>	5 (12.5)	6 (13.6)	1 (2.3)	8 (18.2)	4 (10.8)	5 (10.2)		
<i>P. aeruginosa</i>	3 (7.5)	7 (15.9)	1 (2.3)	3 (6.8)	4 (10.8)	8 (16.3)		
ITT	N=50		N=51		N=44		N=60	
<i>H. influenzae</i>	16 (32.0)	14 (24.1)	13 (25.5)	8 (16.3)	10 (22.7)	14 (23.3)		
<i>M. catarrhalis</i>	5 (10.0)	8 (13.8)	16 (31.4)	13 (26.5)	6 (13.6)	16 (26.7)		
<i>S. pneumoniae</i>	8 (16.0)	5 (8.6)	9 (17.6)	10 (20.4)	6 (13.6)	7 (11.7)		
<i>H. parainfluenzae</i>	7 (14.0)	5 (8.6)	2 (3.9)	0	7 (15.9)	7 (11.7)		
<i>S. aureus</i>	8 (16.0)	7 (12.1)	1 (2.0)	10 (20.4)	4 (9.1)	5 (8.3)		
<i>P. aeruginosa</i>	4 (8.0)	8 (13.8)	3 (5.9)	3 (6.1)	5 (11.4)	10 (16.7)		

Note: Percentages are based on the total number of patients; some patients may have more than one pathogen.

7.4 Results of AECB Clinical Studies

7.4.1 Overall Success Rates

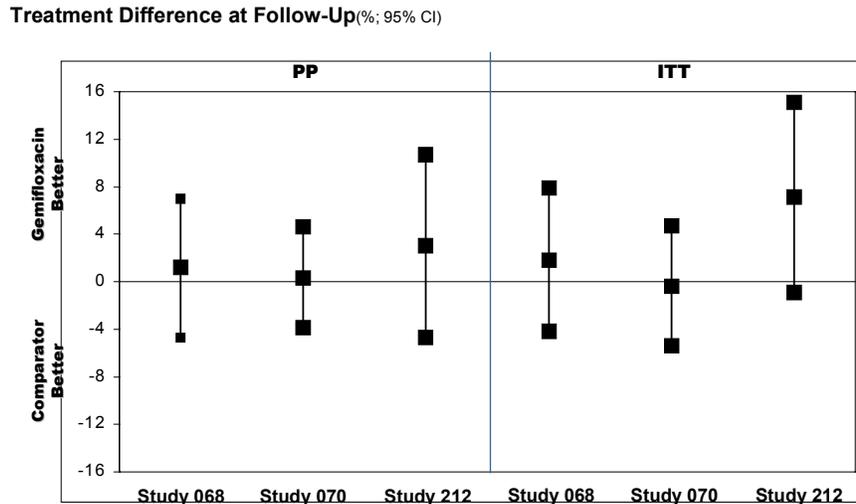
The primary efficacy parameter in the principal AECB studies was the clinical response (success or failure) at follow-up (Day 13 to 24). The results of the clinical response at follow-up for the principal AECB studies clearly demonstrate that gemifloxacin 320 mg PO once daily for 5 days was at least as good as the response for the comparators (i.e., clarithromycin 500 mg bid for 7 days, amoxicillin/clavulanate 500 mg/125 mg tid for 7 days, and levofloxacin 500 mg PO for 7 days) (Table 22 and Figure 5). In each study the lower limit of the 95% confidence interval for the treatment difference (gemifloxacin – comparator) was no less than the pre-defined non-inferiority limit of –10% for Studies 068 and 070 and –13% for Study 212, and in all cases the confidence intervals included 0. Results across these studies provided consistent evidence of efficacy of gemifloxacin.

The results of the ITT population analysis were consistent with the conclusions from the clinical PP population analyses.

Table 22: Clinical Response at Follow-Up (Test of Cure): Principal AECB Studies

Clinical PP Population	Success Rate		Treatment Difference % (95% CI)
	Gemifloxacin % (n/N)	Comparator % (n/N)	
068	86.0 (239/278)	84.8 (240/283)	1.2 (-4.7, 7.0)
070	93.6 (247/264)	93.2 (248/266)	0.3 (-3.9, 4.6)
212	88.2 (134/152)	85.1 (126/148)	3.0 (-4.7, 10.7)

Figure 5: AECB Clinical Response at Follow-Up: Treatment Differences and 95% Confidence Intervals Clinical PP and ITT Population



Results for the bacteriological response at follow-up are shown in Table 23. The results of the bacteriology ITT population were similar to the bacteriology PP population at all 3 visit assessments.

Table 23: Bacteriological Response at Follow-Up (Test of Cure): Principal AECB Studies

Bacteriology PP Population	Success Rate		Treatment Difference % (95% CI)
	Gemifloxacin % (n/N)	Comparator % (n/N)	
068	85.0 (34/40)	72.7 (32/44)	12.3 (-4.9, 29.5)
070	90.9 (40/44)	79.5 (35/44)	11.4 (-3.3, 26.0)
212	78.4 (29/37)	85.7 (42/49)	-7.3 (-23.8, 9.2)

7.4.2 Eradication of *H. influenzae*

In a prospectively defined analysis in Study 068 of a subset of patients with *H. influenzae*, a detailed study of bacterial eradication was conducted by sampling patients with *H. influenzae* recorded at baseline. On days 1 through 6, sputum cultures were obtained before the morning dose of study medication. For each patient the time to bacterial eradication was defined as the time in days to the first day on which there was an outcome of eradication. Eradication was defined as elimination of *H. influenzae* from the repeat sputum culture. Twenty-four of the 193

patients who agreed to undergo daily sputum cultures (12 per treatment group) had an isolate of *H. influenzae* recovered at Day 0. The number (%) of patients with a bacteriological outcome of persistence of *H. influenzae* over time is shown in Table 24.

Table 24: Number (%) of Patients with Response of Bacterial Persistence by Day in AECB Study 068

Timepoint	Persistence (%)	
	Gemifloxacin 320 mg PO x 5 days	Clarithromycin 500 mg bid x 7 days
Day 0	12 (0%)	12 (0%)
Day 1	0 (100%)	6 (50%)
Day 2	0 (100%)	3 (75%)
Day 3	0 (100%)	3 (75%)
Day 4	0 (100%)	2 (83%)
Day 5	0 (100%)	1 (92%)
Day 6	0 (100%)	1 (92%)

The median time to eradication of *H. influenzae* in sputum samples was calculated. Treatment with gemifloxacin resulted in statistically significantly faster time to eradication of *H. influenzae*, compared with clarithromycin ($p = 0.02$). The median time to eradication was 1 day in the gemifloxacin group and 2 days in the clarithromycin group.

The proportion of patients with a bacteriological outcome of eradication for *H. influenzae* on Day 1 was 58% (7/12) in the gemifloxacin group and 25% (3/12) in the clarithromycin group [95% CI; -3.8, 70.5] (Note that the bacteriological outcome of eradication did not include the 5 patients in the gemifloxacin group and 3 patients in the clarithromycin group that were assigned an outcome of unable to determine, as a sputum sample could not be obtained).

7.4.3 Subgroup Analyses

The clinical success rates at follow-up in the various demographic subgroups (age, gender, and race) were in general accordance with the response rates observed in the total patient population. The clinical success rates in the combined principal study database (clinical PP follow-up population) for the subgroup of patients with severe Stage 3 AECB were still high (82.1% for patients in the gemifloxacin group), although slightly lower than for patients with Stage 2 AECB (89.8%). Overall clinical success rates were 86% for heavy smokers (smoking pack years >30) and 92% for lighter smokers (smoking pack years >0-30). No clinically important differences were noted between treatment groups.

7.4.4 Supportive Clinical Studies in AECB - Studies 069 and 207

The study populations of Studies 069 and 207 were representative of the general AECB population and similar to the populations recruited into the principal clinical studies. Similar to the principal studies, *H. influenzae* was the most prevalent pathogen isolated. Study 069 evaluated the effectiveness of gemifloxacin versus a potent quinolone, trovafloxacin, however, the comparator trovafloxacin dose regimen of 200 mg od for 5 days was not the same as the approved dose (100 mg od for 7-10 days) in the U.S. Study 207 was an open but controlled trial that evaluated gemifloxacin's effectiveness as an oral treatment versus parenteral treatment ceftriaxone 1 g IV followed by cefuroxime 500 mg twice daily in patients hospitalized with AECB.

In Study 069, the clinical success rates at follow-up in the PP population were 92% (249/272) in the gemifloxacin group and 88% (241/275) in the trovafloxacin group (95% CI for treatment difference: -1.2, 9.0). The bacteriological response rates at follow-up in the PP population were 87% (46/53) in the gemifloxacin group and 82% (42/51) in the trovafloxacin group (95% CI for treatment difference: -9.4, 18.3). The clinical success rates at follow-up in the ITT population were 89% (270/302) in the gemifloxacin group and 83% (261/314) in the trovafloxacin group (95% CI for treatment difference: 0.9, 11.7). As the 95% CI for the treatment difference did not cross zero (95% CI for the treatment difference: 0.9, 11.7), the clinical efficacy of gemifloxacin was concluded to be statistically significantly superior to that of trovafloxacin in this population. The bacteriological efficacy of gemifloxacin in Study 069 was concluded to be at least as good as trovafloxacin at follow-up.

The results of Study 207 indicated that gemifloxacin 320 mg PO once daily for 5 days was at least as effective as parenteral ceftriaxone 1 g IV followed by cefuroxime 500 mg twice daily when given orally for the treatment of AECB. The clinical success rate at follow-up in clinically evaluable patients was 87% in the gemifloxacin group and 81% in the ceftriaxone/cefuroxime group (95% CI for treatment difference: -3.9, 14.9). In addition the clinical response at follow-up for the clinical ITT population in the group receiving gemifloxacin was statistically superior to the ceftriaxone/cefuroxime group of patients (gemifloxacin, 83% and ceftriaxone/cefuroxime 72%), (95% CI for treatment difference: 0.7, 20.4).

The bacteriological response at follow-up in the PP population was 30/47 (63.8%) patients in the gemifloxacin group and 28/41 (68.3%) patients in the ceftriaxone/cefuroxime group. The treatment difference was -4.5% (95% CI -24.3, 15.3). The bacteriological response rates for the follow-up ITT population were 30/48 (62.5%) and 31/51(60.8%), respectively, with a treatment difference of 1.7% (95% CI -17.4, 20.9).

An important clinical outcome in Study 207, for the clinical ITT population, the time to discharge from hospital was statistically shorter for the patients treated with gemifloxacin than for patients treated with ceftriaxone/cefuroxime (p= 0.04, Wilcoxon test) (Table 25). The median time to discharge from the hospital was 2 days shorter for patients treated with gemifloxacin 320 mg PO than for patients treated with ceftriaxone IV 1 g/cefuroxime 500 mg bd, 9 vs. 11 days, respectively.

Table 25: Time to Discharge from Hospital (Clinical ITT population) in Study 207

	Treatment Group	
	Gemifloxacin 320 mg PO	Ceftriaxone iv 1 g/ Cefuroxime 500 mg bd
	N=138	N=136
Number of patients discharged from hospital [n (%)]	120 (87.0)	111 (81.6)
Median time to discharge from hospital (days)	9	11
Hazard Ratio* (CI) P value	0.83 (0.64, 1.07) p=0.04	

* Kaplan-Meier estimate

The results of the secondary efficacy parameters in the supportive studies, including clinical response at the end of therapy and long-term follow-up, along with bacteriological response at the end of therapy and long-term follow-up, were supportive of gemifloxacin efficacy.

7.4.5 Results of Eradication of Key Pathogens Associated with AECB

Eradication or presumed eradication rates for each of the 5 key pathogens (*H. influenzae*, *M. catarrhalis*, *S. pneumoniae*, *H. parainfluenzae*, *S. aureus*) identified at screening in the principal and supportive (5-day) AECB clinical trials were consistently high (Table 26). In the bacteriology PP population at follow-up, the overall pathogen eradication rates (eradicated and presumed eradicated) were 75.2% in the combined gemifloxacin group and 72.0% for the combined all comparators group. At end of therapy, 86.8% of initial pathogens in the combined gemifloxacin group were either eradicated or presumed eradicated in the PP population compared with 84.1% pathogens in the combined all comparators group. The results for the combined bacteriology ITT population were similar to the combined bacteriology PP population.

Table 26: Pre-Therapy Pathogens Eradicated or Presumed Eradicated at End of Therapy and Follow-Up: AECB Combined Studies

	Combined AECB studies							
	068, 069, 070, 105, 207, 212							
	Bacteriology PP**				Bacteriology ITT			
	Gemifloxacin		All Comparators		Gemifloxacin		All Comparators	
Follow-Up	N=287		N=287		N=314		N=334	
	n/N*	%	n/N*	%	n/N*	%	n/N*	%
All Pathogens	261/347	(75.2)	250/347	(72.0)	271/378	(71.7)	272/403	(67.5)
<i>H. influenzae</i>	77/87	(88.5)	66/97	(68.0)	81/94	(86.2)	70/107	(65.4)
<i>M. catarrhalis</i>	43/49	(87.8)	43/48	(89.6)	44/53	(83.0)	44/54	(81.5)
<i>S. pneumoniae</i>	37/45	(82.2)	35/47	(74.5)	39/50	(78.0)	40/54	(74.1)
<i>H. parainfluenzae</i>	28/63	(44.4)	26/45	(57.8)	29/65	(44.6)	29/52	(55.8)
<i>S. aureus</i>	13/19	(68.4)	21/25	(84.0)	15/23	(65.2)	23/28	(82.1)
End of Therapy	N=293		N=300		N=314		N=334	
	n/N*	%	n/N*	%	n/N*	%	n/N*	%
All Pathogens	308/355	(86.8)	307/365	(84.1)	320/378	(84.7)	327/403	(81.1)
<i>H. influenzae</i>	87/90	(96.7)	85/102	(83.3)	90/94	(95.7)	89/107	(83.2)
<i>M. catarrhalis</i>	50/51	(98.0)	48/52	(94.1)	51/53	(96.2)	49/54	(90.7)
<i>S. pneumoniae</i>	45/47	(95.7)	46/50	(92.0)	47/50	(94.0)	49/54	(90.7)
<i>H. parainfluenzae</i>	39/63	(61.9)	33/47	(70.2)	40/65	(61.5)	35/52	(67.3)
<i>S. aureus</i>	17/20	(85.0)	22/25	(88.0)	20/23	(87.0)	24/28	(85.7)

Note: Failures at End of Therapy were carried forward as Failures at Follow-Up.

* n/N = number of pathogens eradicated or presumed eradicated/number of pathogens.

** Bacteriology PP population at end of therapy or follow-up

7.4.6 Other Studies in AECB

Data from 5 supportive studies (Studies 105, 112, and 139 - 5 Day Treatment Regimen and Studies 008 and 061 - 7 Day Treatment Regimen) supported the conclusions observed in the pivotal AECB studies and in Studies 069 and 207 summarized previously.

7.4.6.1 Long-Term Follow-up of Study 068 (Study 139)

Study 139 was the long-term follow up of the pivotal Study 068. This included U.S. and Canadian participants only. The primary clinical evaluation was the proportion of patients at each visit in the ITT population who had resolved from their initial episode of AECB and had not yet had a recurrence requiring antimicrobial therapy. The long-term study included 438 patients. The treatment differences are summarized in Table 27 for the ITT population.

Table 27: The Proportions of Patients with No Recurrences after Resolution of the Initial Episode of AECB in Study 139 at Each Visit

Visit	Week	Gemifloxacin 320 mg PO		Clarithromycin 500 mg bid		Treatment Difference* (95% CI)	P-value
		n (%)	N	n (%)	N		
Visit 2	4 to 5	176 (87.1)	202	173 (80.8)	214	6.3 (-0.7, 13.3)	0.081
Visit 3	12	148 (80.9)	183	131 (74.4)	176	6.4 (-2.2, 15.1)	0.143
Visit 4	26	120 (71.0)	169	100 (58.5)	171	12.5 (2.5, 22.6)	0.016

* Gemifloxacin – Clarithromycin

There were treatment differences in favor of gemifloxacin at all visits, and the proportion of patients with no recurrence of AECB after resolution of their initial episode was clinically and significantly higher at the pre-defined endpoint for analysis, 26 weeks (Visit 4) in the gemifloxacin group than in the clarithromycin group (p = 0.016).

The number of patients hospitalized for RTI-related episodes over the 26-week study period favored the gemifloxacin group compared with the clarithromycin group [5/214 (2.3%) vs. 14/224 (6.3%)]. The treatment difference in favor of gemifloxacin was -3.91% [95% CI (-7.67%, -0.15%); P = 0.059]. Some patients had more than one hospitalization episode, but similarly, there were fewer hospitalizations for RTI over the study period among patients treated with gemifloxacin than among patients treated with clarithromycin [7/214 (3.3%) vs. 16/224 (7.1%)]. The treatment difference in favor of gemifloxacin was -3.87% [95% CI (-8.00%, 0.26%); P = 0.087]. The length of RTI related hospital stay, the number of days on antibiotic/RTI-related antibiotic therapy, and the number of RTI-related physician visits showed no differences between the treatment groups.

7.4.6.2 Study 112

A second study, Study 112, with a different primary endpoint, 4-month follow-up, and conducted principally over the summer months, failed to replicate this effect; however, relapse rates in both groups were low, potentially due to the time of year. However, there were some major inconsistencies across countries. When analyzed by country, statistically significant effects were observed by treatment group in favor of gemifloxacin. For example, the results from sites in the United Kingdom looked similar to those reported above for Study 139.

7.5 Conclusions from AECB studies

Oral gemifloxacin once daily for 5 days achieves high clinical and bacteriological success rates in patients with AECB. Gemifloxacin is highly effective in the eradication of the major

pathogens associated with AECB. In a study where samples were collected daily, gemifloxacin eradicated *H. influenzae* faster than clarithromycin comparator. This is particularly important in light of growing resistance. Since longer regimens of antibiotics play an important role in promoting antimicrobial resistance, shorter treatment courses can be used as an important step to help slow the emergence of anti-microbial resistance.

Gemifloxacin also demonstrates improvement in clinical outcome parameters. In the long-term follow-up of pivotal study 068 (Study 139), gemifloxacin keeps more patients recurrence free. In addition, fewer patients are hospitalized due to RTI-related episodes than in the clarithromycin group. And gemifloxacin patients spend less time in the hospital than IV-PO cephalosporin-treated patients (Study 207).

Overall, the results demonstrate that gemifloxacin administered orally for 5 days is an effective antibacterial treatment for AECB. No intravenous treatment is necessary. The data support the indication of gemifloxacin at a dose of 320 mg PO for 5 days for the treatment of AECB due to *H. influenzae*, *M. catarrhalis*, *S. pneumoniae*, *H. parainfluenzae*, and *S. aureus*.

8. REVIEW OF GEMIFLOXACIN EFFICACY IN COMMUNITY-ACQUIRED PNEUMONIA

8.1 Background and Rationale

CAP continues to be a common and serious illness in the U.S. The 3 to 4 million annual reported cases of CAP result in approximately 10 million physician visits, 600,000 hospitalizations, 64 million days of restricted activity, and 64,000 deaths annually, making pneumonia the seventh leading cause of death in the U.S., and the most common cause of death due to infectious disease (Marrie 1998; CDC 2002). Hospitalizations for CAP are estimated to occur at an incidence of 258 cases per 100,000 of the general population and are higher in the elderly at 962 cases per 100,000 persons ≥ 65 years of age (Bartlett et al. 1998).

CAP is defined as an acute infection of the pulmonary parenchyma that is associated with at least some symptoms of acute infection and is accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia (such as altered breath sounds and/or localized rales). It also requires that it occurs in a patient who is not hospitalized or residing in a long-term-care facility for ≥ 14 days before the onset of symptoms. The clinical definition of CAP requires at least two symptoms of acute lower respiratory infection, including fever or hypothermia, rigors, sweats, new cough (with or without sputum production), or change in the color of respiratory secretions in a patient with chronic cough, chest discomfort, or the onset of dyspnea (Bartlett et al. 1998).

CAP may be caused by a variety of pathogens although in a high proportion of cases (40%-60% across published studies) the etiology can remain uncertain (Bartlett et al. 1998). The most common etiologic agents of CAP are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pyogenes*, and *Staphylococcus aureus*, as well as intracellular pathogens such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella* species (Bartlett et al. 1998).

Antibiotics are the mainstay of treatment for most patients with pneumonia, and where possible, antibiotic treatment should be specific and individualized. However, since the responsible pathogen is not identified in a high proportion of patients with CAP, an empiric approach is usually necessary. Until relatively recently, *S. pneumoniae*, was nearly uniformly susceptible to penicillin which permitted the use of penicillin G alone for the treatment of pneumococcal infection, without testing for drug susceptibility. Over the last decade, resistance to penicillin and macrolides has increased sufficiently so that alternative agents, such as fluoroquinolones, with more predictable activity against resistant organisms are now recommended (Doern 1995; Butler et al. 1996; Doern et al. 1996; Cunha and Shea 1998). For empiric antibiotic treatment of CAP, the recent recommendations of IDSA for first-line therapy include the fluoroquinolones and macrolides (Bartlett et al. 1998). Unfortunately, resistance to fluoroquinolones has emerged. The clinical significance of quinolone resistant *S. pneumoniae* has been highlighted in recent

reports of levofloxacin resistant pneumococcal pneumonia, leading to treatment failure and death. In these studies, all baseline isolates, where collected, were susceptible to gemifloxacin and isolates from 5 of 8 patients remained susceptible to gemifloxacin following emergence of levofloxacin resistance (Davidson 2002; Low 2002). The last isolate, collected from the patient who died, was gemifloxacin susceptible. All levofloxacin resistant organisms were either resistant or intermediate to moxifloxacin and gatifloxacin (Anderson et al. 2002; Davidson et al. 2002; Ross et al 2002).

Gemifloxacin represents an attractive alternative to other antibiotics used in the treatment of CAP, including the fluoroquinolones, because of its high antimicrobial potency, activity against resistant pneumococci, and convenient oral dosing. Additionally, there is no requirement for an intravenous to oral switch for more severe disease, thereby keeping patients, in particular the elderly, mobile.

8.2 Overview of Gemifloxacin Studies in CAP

The clinical program to evaluate the efficacy of gemifloxacin in the treatment of CAP consists of four pivotal studies, including 3 double-blind, randomized, actively-controlled clinical studies (Studies 011, 012, and 049) and one open, actively-controlled study (Study 185). In addition, two uncontrolled studies (Studies 061 and 287) were conducted. These studies encompass a large clinical experience with gemifloxacin; a total of 1349 patients with CAP have received treatment with gemifloxacin 320 mg PO once daily, and 927 patients with CAP have received treatment with active comparator. These studies, grouped as controlled and uncontrolled studies, are outlined below in Table 28.

Table 28: CAP: Controlled and Uncontrolled Studies of Gemifloxacin

Study	Study Title	Treatment Regimen	Duration	N*	Geographic Region
Controlled studies					
011	SB-265805/RSD-100ZW1/1 SB-265805/011. A Randomized, Double-Blind, Double-Dummy, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Oral Gemifloxacin 320 mg Once Daily for Seven Days Versus Oral Amoxicillin/Clavulanate 1 g/125 mg Three Times Daily for 10 Days for the Treatment of Community Acquired Pneumonia of Suspected Pneumococcal Origin	gemifloxacin 320 mg PO	7 days	168	Europe, S. Africa
		amoxicillin/clavulanate 1 g/125 mg tid	10 days	156	
012	SB-265805/RSD-100ZW2/1 SB-265805-012. A Randomized, Double-Blind, Double-Dummy, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Oral Gemifloxacin 320 mg Once Daily Versus Oral Cefuroxime 500 mg Plus Oral Clarithromycin 500 mg Twice Daily for 7 or 14 days in the Treatment of Bacterial Community Acquired Pneumonia (CAP) in Adults	gemifloxacin 320 mg PO	7 or 14 days	319	U.S. Canada, Europe, S. Africa
		cefuroxime 500 mg /clarithromycin 500 mg bid	7 or 14 days	322	
049	SB-265805/RSD-101NG8/1 SB-265805/049. A Randomized, Double-Blind, Double-Dummy, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Oral Gemifloxacin 320 mg Once Daily Versus Oral Trovafloxacin 200 mg Once Daily for 7 or 14 Days in the Treatment of Bacterial Community Acquired Pneumonia (CAP) in Adults	gemifloxacin 320 mg PO	7 or 14 days	290	U.S., Mexico, Spain
		trovafloxacin 200 mg PO	7 or 14 days	281	
185	SB-265805/RSD-1017ZT/1. SB-265805/185. A Randomized, Open, Multicenter Study to Compare the Efficacy, Safety and Tolerability of Oral Gemifloxacin Versus Intravenous Ceftriaxone (with or without Macrolide) Followed by Oral Cefuroxime (with or without Macrolide) in the Treatment of Hospitalized Adult Patients with Community Acquired Pneumonia (CAP)	gemifloxacin 320 mg PO	7-14 days	172	Australia, Europe, Guatemala, Lebanon, Philippines, Singapore and N. America
		IV ceftriaxone 2 g PO + cefuroxime 500 mg PO bid**	1-7 days + 1-13 days (IV/PO= \leq 14)	173	
Uncontrolled studies					
061	SB-265805/RSD-100ZW4/1 SB-265805/061. An Open, Non-Comparative, Multicenter Study to Assess the Efficacy and Safety of Oral Gemifloxacin 320 mg Once Daily for Seven Days for the Treatment of Lower Respiratory Infections in Adults	gemifloxacin 320 mg PO	7 days	216§	World-Wide (Except N. America)

Study	Study Title	Treatment Regimen	Duration	N*	Geographic Region
287	SB-265805/RSD-101N9K/1 SB-265805/287. An Open Label, Non-Comparative Study to Assess the Efficacy and Safety of Oral Gemifloxacin 320 mg, Once Daily for Seven Days, for the Treatment of Community Acquired Pneumonia of Suspected Pneumococcal Origin in Countries with a High Prevalence of Drug-Resistant Respiratory Pathogens	gemifloxacin 320 mg PO	7 days	188	Asia, U.S., Mexico, Philippines

* N refers to the number of randomized patients (enrolled for uncontrolled studies); N= number of patients with CAP.

** Both comparator treatments were administered with or without macrolide

§ Study 061 was conducted in patients with CAP or AECB.

Studies 011, 012, and 049 were all randomized, multicenter, double-blind, double-dummy, parallel group studies designed to evaluate the clinical and antibacterial efficacy and safety of gemifloxacin in comparison with antibacterial regimens selected from major antibiotic classes.

Study 011 was designed to enroll patients with CAP of suspected pneumococcal origin. A 10-day treatment course of high dose amoxicillin/clavulanate was selected as the comparator, due to the proven activity of this agent against *S. pneumoniae* and β -lactamase-producing organisms (Neu et al. 1993). The dose of amoxicillin in the combination used (amoxicillin/clavulanate 1 g/125 mg tid) was higher than the approved doses in the U.S. for the treatment of CAP (i.e., 875/125 mg bid or 500/125 mg tid) when the study was first conducted (Augmentin package insert 1999). This dose, chosen to be consistent with the highest dose recommendations in the countries where the study was conducted, is widely considered to be a gold standard for the treatment of CAP due to *S. pneumoniae*, and therefore represents a greater challenge for demonstrating gemifloxacin efficacy in a comparative study with this agent.

In Study 012, the comparator regimen consisted of agents with activity against atypical pathogens. Cefuroxime axetil (a β -lactam) was administered in combination with clarithromycin (a macrolide), in order to cover both the so-called typical and atypical organisms, including macrolide-resistant and β -lactam-resistant organisms,

In Study 049, the comparator regimen consisted of agents with activity against atypical pathogens. Trovafloxacin, a quinolone with potent activity against respiratory pathogens, particularly *S. pneumoniae* was selected as the comparator (Trovan package insert 1997).

Study 185 was an open label, randomized, multicenter, parallel group study designed to evaluate the clinical and antibacterial efficacy and safety of gemifloxacin in comparison with a parenteral therapy in patients hospitalized at screening.

Study 287 was ongoing at the time the NDA resubmission was filed but it was designed as an open label non-randomized study to evaluate the clinical and antibacterial efficacy of gemifloxacin against primarily antibiotic resistant *S. pneumoniae*.

Male and female patients aged ≥ 18 years were recruited into the studies if they met eligibility criteria based on the definitions of CAP as determined from FDA and European guidelines (Chow et al. 1992; FDA 1997; CPMP 1997).

8.3 Demographic and Baseline Characteristics

The demographic and baseline characteristics of patients in the gemifloxacin CAP studies are summarized in Table 29 (clinical PP population) and Table 30 (ITT population) for the combined study datasets (i.e., controlled studies, uncontrolled studies, and all studies).

In all of the CAP clinical studies, 4 patient populations were defined for the analysis of clinical, radiological, and bacteriological efficacy as follows:

ITT: with the exception of Study 185, all randomized patients who took at least one dose of study medication. In Study 185, all randomized patients were included to reduce potential bias associated with the open design.

Clinical PP: a subset of the ITT population that excluded patients who violated the protocol to an extent that could affect treatment efficacy.

Bacteriology ITT: a subset of the ITT population that included patients with evidence of infection, with at least one pre-therapy pathogen identified at screening.

Bacteriology PP: a subset of the Bacteriology ITT population (i.e., all patients had at least one pre-therapy pathogen), which excluded patients who violated the protocol to an extent that could affect treatment efficacy.

Patients were excluded from the PP populations only from the time that the violation occurred. Hence, the Clinical PP and Bacteriology PP populations may have contained different numbers of patients at end of therapy and follow-up.

Overall, there were 14 patients with penicillin-resistant *S. pneumoniae* (PRSP) (penicillin MIC ≥ 2 $\mu\text{g/mL}$).

Severity of CAP was determined by categorizing patients according to the mortality risk classes published by Fine et al. (1997). Patients were assigned to one of the 5 classes (I, II, III, IV, and V) with respect to risk of death within 30 days, firstly according to an algorithm (class I) and then on the basis of a total points score (classes II-V).

Based on the assigned risk class, patients were classified as having mild, moderate, or severe CAP, as summarized in Table 31 and Table 32.

For the combined controlled studies, the majority of patients had CAP of mild severity (risk class I and II). Approximately 10% of patients had severe CAP in this population. The proportions of patients with mild, moderate, and severe CAP were similar between the combined gemifloxacin group and the combined comparator group. A slightly lower proportion of patients (approximately 5%) had severe CAP in the combined uncontrolled studies population.

Other factors indicative of CAP severity were also considered. Approximately 58% of the combined controlled studies population and 51% of the combined uncontrolled study population was hospitalized at screening. The proportion of patients who were hospitalized varied across

the studies from all patients in Study 185 and 94% in Study 011, to 27% in Study 049. The proportion of patients who were bacteremic was approximately 5% in the combined controlled studies and approximately 4% in the uncontrolled studies. Taken together, approximately 60% of the controlled study population and 53% of the uncontrolled study population were patients who had severe CAP, were hospitalized, or were bacteremic.

Table 29: Demographic and Baseline Characteristics: CAP Combined Datasets (Clinical PP Follow-Up Population)

Demographic/Baseline Characteristic	Controlled Studies				Uncontrolled Studies		All Studies			
	Studies 011, 012, 049 and 185				Studies 061 and 287		Controlled + Uncontrolled			
	Gemifloxacin 320 mg PO		Pooled Comparators		Gemifloxacin 320 mg PO		Gemifloxacin 320 mg PO		Pooled Comparators	
	N=697		N=698		N=315		N=1012		N=698	
Gender: n (%)										
Male	401	(57.5)	400	(57.3)	148	(47.0)	549	(54.2)	400	(57.3)
Female	296	(42.5)	298	(42.7)	167	(53.0)	463	(45.8)	298	(42.7)
Race: n (%)										
White	641	(92.0)	633	(90.7)	90	(28.6)	731	(72.2)	633	(90.7)
Black	28	(4.0)	40	(5.7)	10	(3.2)	38	(3.8)	40	(5.7)
Oriental	11	(1.6)	10	(1.4)	127	(40.3)	138	(13.6)	10	(1.4)
Other*	17	(2.4)	15	(2.1)	88	(27.9)	105	(10.4)	15	(2.1)
Age										
Mean (SD)	54.2 (18.34)		53.6 (18.31)		50.5 (18.32)		53.1 (18.41)		53.6 (18.31)	
Range	18-94		18-97		18-89		18-94		18-97	
CAP Severity/Fine Criteria**										
Mild/Risk Class I-II	498	(71.4)	493	(70.6)	257	(81.6)	755	(74.6)	493	(70.6)
Moderate/Risk Class III	121	(17.4)	138	(19.8)	45	(14.3)	166	(16.4)	138	(19.8)
Severe/Risk Class IV-V	78	(11.2)	67	(9.6)	13	(4.1)	91	(9.0)	67	(9.6)
Hospitalized, n (%)	396	(56.8)	411	(58.9)	157	(49.8)	553	(54.6)	411	(58.9)
Bacteremic Patients, n (%)	35	(5.0)	37	(5.3)	13	(4.1)	48	(4.7)	37	(5.3)
Severe CAP, Hospitalized or Bacteremic, n (%)	410	(58.8)	428	(61.3)	164	(52.1)	574	(56.7)	428	(61.3)
Patients with PRSP, n (%)	6	(0.9)	4	(0.6)	6	(1.9)	12	(1.2)	4	(0.6)

Table 30: Demographic and Baseline Characteristics: CAP Combined Datasets (ITT Population)

Demographic/Baseline Characteristic	Controlled Studies				Uncontrolled Studies		All Studies			
	Studies 011, 012, 049 and 185				Studies 061 and 287		Controlled + Uncontrolled			
	Gemifloxacin 320 mg PO		Pooled Comparators		Gemifloxacin 320 mg PO		Gemifloxacin 320 mg PO		Pooled Comparators	
	N=947		N=927		N=402		N=1349		N=927	
Gender: n (%)										
Male	534	(56.4)	537	(57.9)	188	(46.8)	722	(53.5)	537	(57.9)
Female	413	(43.6)	390	(42.1)	214	(53.2)	627	(46.5)	390	(42.1)
Race: n (%)										
White	849	(89.7)	823	(88.8)	109	(27.1)	958	(71.0)	823	(88.8)
Black	51	(5.4)	65	(7.0)	11	(2.7)	62	(4.6)	65	(7.0)
Oriental	18	(1.9)	17	(1.8)	163	(40.5)	181	(13.4)	17	(1.8)
Other	29	(3.1)	22	(2.4)	119	(29.6)	148	(11.0)	22	(2.3)
Age										
Mean (SD)	54.1 (18.47)		53.5 (18.51)		51.1 (18.27)		53.2 (18.45)		53.5 (18.51)	
Range	18-97		18-97		18-89		18-97		18-97	
CAP Severity/Fine Criteria										
Mild/Risk Class I-II	676	(71.4)	653	(70.4)	320	(79.6)	996	(73.8)	653	(70.4)
Moderate/Risk Class III	163	(17.2)	179	(19.3)	61	(15.2)	224	(16.6)	179	(19.3)
Severe/Risk Class IV-V	108	(11.4)	95	(10.2)	21	(5.2)	129	(9.6)	95	(10.2)
Hospitalized, n (%)	556	(58.7)	539	(58.1)	204	(50.7)	760	(56.3)	539	(58.1)
Bacteremic Patients, n (%)	47	(5.0)	53	(5.7)	15	(3.7)	62	(4.6)	53	(5.7)
Severe CAP, Hospitalized or Bacteremic, n (%)	571	(60.3)	563	(60.7)	213	(53.0)	784	(8.1)	563	(60.7)
Patients with PRSP, n (%)	7	(0.7)	4	(0.4)	7	(1.7)	14	(1.0)	4	(0.4)

Table 31: Assessment of CAP Severity: Stratification of Risk Score

CAP Severity	Risk Class	Based On*
Mild	I	Absence of risk factors**
	II	≤ 70 total points
Moderate	III	71 – 90 total points
Severe	IV	91 – 130 total points
	V	>130 total points

* The scoring system for assigning points is summarized in Table 32.

**Risk factors were age >50 years, 5 coexisting illnesses (neoplastic disease, congestive heart failure, cerebrovascular disease, renal disease, and liver disease), and 5 physical examination findings (altered mental status, pulse ≥125/minute, respiratory rate ≥30/minute, systolic blood pressure <90 mmHg, and temperature <35°C or ≥40°C)

Table 32: Point Scoring System for Assignment to Risk Classes II, III, IV, and V

Characteristic	Points Assigned*
Demographic factor	
Age	
Men	Age (yr)
Women	Age (yr) - 10
Nursing home resident	+10
Coexisting illnesses†	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Physical examination findings	
Altered mental status‡	+20
Respiratory rate ≥ 30 /min	+20
Systolic blood pressure < 90 mmHg	+20
Temperature $< 35^{\circ}\text{C}$ or $\geq 40^{\circ}\text{C}$	+15
Pulse ≥ 125 /min	+10
Laboratory and radiographic findings	
Arterial pH < 7.35	+30
Blood urea nitrogen ≥ 30 mg/dL (11 mmol/L)	+20
Sodium < 130 mmol/L	+20
Glucose ≥ 250 mg/dL (14 mmol/L)	+10
Hematocrit $< 30\%$	+10
Partial pressure of arterial oxygen < 60 mmHg	+10
Pleural effusion	+10

Fine et al. 1997

*A total point score for a given patient is obtained by summing the patient's age in years (age minus 10 for women) and the points for each applicable characteristic. The points assigned to each predictor variable were based on coefficients obtained from the logistic-regression model used in step 2 of the prediction rule (see the Methods section of Fine et al. 1997).

†Neoplastic disease is defined as any cancer except basal or squamous cell cancer of the skin that was active at the time of presentation or diagnosed within 1 year of presentation. Liver disease is defined as a clinical or histologic diagnosis of cirrhosis or another form of chronic liver disease such as chronic active hepatitis. Congestive heart failure is defined as systolic or diastolic ventricular dysfunction documented by history, physical examination, and chest radiograph, electrocardiogram (ECG), multiple gated acquisition scan, or left ventriculogram. Cerebrovascular disease is defined as a clinical diagnosis of stroke or transient ischemic attack or stroke documented by magnetic resonance imaging or computed tomography. Renal disease is defined as a history of chronic renal disease or abnormal blood urea nitrogen and creatinine concentrations documented in the medical record.

‡Altered mental status is defined as disorientation with respect to person, place, or time that is not known to be chronic, stupor, or coma.

8.4 Results of CAP Clinical Studies

8.4.1 Overall Success Rates

Overall clinical, bacteriological, and radiological success rates for the CAP clinical studies are summarized in Table 33, 34, and 35, respectively. Clinical response (success or failure) at follow-up (test of cure) was the primary efficacy parameter in the controlled CAP studies (Studies 011, 012, 049, and 185) and in the uncontrolled Study 061. In the uncontrolled Study 287, clinical response at follow-up was a secondary efficacy parameter.

At follow-up in the 4 controlled clinical studies, treatment with gemifloxacin 320 mg once daily resulted in high clinical response rates. The proportion of gemifloxacin treated patients with a clinical response of success ranged between 87.6% and 94.0% and for the comparator groups between 87.6% and 93.4% (clinical PP populations).

The clinical success rates at follow-up in Studies 011, 049, and 185 clearly demonstrate that treatment with gemifloxacin 320 mg once daily was at least as good as the comparators' regimens (i.e., the oral regimens of trovafloxacin 200 mg PO and amoxicillin/clavulanate 1 g/125 mg tid, and the consecutive regimen of intravenous ceftriaxone followed by oral cefuroxime). The clinical success rates at follow-up in Study 012 were slightly lower than the comparator cefuroxime axetil plus clarithromycin.

Of note, in Study 011 withdrawals due to treatment failure were higher in the Augmentin group.

Table 33: Summary of Clinical Success Rates at Follow-Up: CAP Studies

	Success Rate		Treatment Difference % (95% CI)*
	Gemifloxacin	Comparator	
	% (n/N)	% (n/N)	
CLINICAL PP			
Controlled Studies			
Study 011	88.7% (102/115)	87.6% (99/113)	1.1 (-7.3, 9.5)
Study 012	87.6% (220/251)	92.6% (238/257)	-5.0 (-10.1, 0.2)
Study 049	94.0% (203/216)	89.9% (186/207)	4.1 (-1.1, 9.3)
Study 185	92.2% (107/116)	93.4% (113/121)	-1.2 (-7.7, 5.4)
Pooled 011/012/049/185 ⁺	90.5% (631/697)	91.1% (636/698)	-0.3 (-4.7, 4.0)
Uncontrolled Studies			
Study 061	91.7% (154/168)	-	(86.1, 95.2)
Study 287	89.8% (132/147)	-	(84.9, 94.7)
ITT			
Controlled Studies			
Study 011	77.2% (129/167)	79.1% (121/153)	-1.8 (-10.9, 7.2)
Study 012	78.4% (250/319)	84.7% (272/321)	-6.4 (-12.4, -0.4)
Study 049	87.5% (253/289)	81.1% (227/280)	6.5 (0.5, 12.4)
Study 185	75.6% (130/172)	78.6% (136/173)	-3.03 (-11.89, 5.83)
Pooled 011/012/049/185 ⁺	80.5% (762/947)	81.6 (756/927)	-1.02 (-7.44, 5.39)
Uncontrolled Studies			
Study 061	82.9% (179/216)	-	(77.0, 87.5)
Study 287	78.5% (146/186)	-	(72.6, 84.4)

* For uncontrolled studies, the 95% CI around the success rate is shown

+The treatment difference and 95% CI were generated using a random effects meta-analysis technique so the pooled treatment difference will not necessarily correspond to the difference in observed gemifloxacin and ‘All Comparators’ response.

Table 34: Summary of Bacteriological Response at Follow-Up: CAP Studies

	Success Rate		Treatment Difference % (95% CI)*
	Gemifloxacin	Comparator	
	% (n/N)	% (n/N)	
BACTERIOLOGY PP			
Controlled Studies			
Study 011	87.2% (41/47)	89.1% (41/46)	-1.9 (-15.0, 11.2)
Study 012	89.9% (71/79)	88.9% (80/90)	1.0 (-8.3, 10.3)
Study 049	87.8% (79/90)	89.3% (67/75)	-1.6 (-11.3, 8.2)
Study 185	90.6% (58/64)	87.3% (55/63)	3.3 (-7.6, 14.2)
Pooled 011/012/049/185 ⁺	88.9% (249/280)	88.7% (243/274)	0.33 (-4.9, 5.6)
Uncontrolled Studies			
Study 061	87.3% (48/55)	-	(74.9, 94.3)
Study 287	90.0% (72/80)	-	(83.4, 96.6)

*For uncontrolled studies, the 95% CI around the success rate is shown.

+The treatment difference and 95% CI were generated using a random effects meta-analysis technique so the pooled treatment difference will not necessarily correspond to the difference in observed Gemifloxacin and 'All Comparators' response.

Table 35: Summary of Radiological Success Rates at Follow-Up: CAP Studies (Clinical PP Population)

	Success Rate		Treatment Difference % (95% CI)*
	Gemifloxacin	Comparator	
	% (n/N)	% (n/N)	
Controlled Studies			
Study 011	90.4% (104/115)	87.6% (99/113)	2.8 (-5.3, 10.9)
Study 012	89.2% (224/251)	94.2% (242/257)	-4.9 (-9.7, -0.1)
Study 049	94.0% (202/215)	90.8% (188/207)	3.1 (-1.9, 8.2)
Study 185	87.9% (102/116)	90.9% (110/121)	-3.0 (-10.8, 4.9)
Pooled 011/012/049/185	90.7% (632/697)	91.5% (639/698)	
Uncontrolled Studies			
Study 061	92.9% (156/168)	-	(87.6, 96.1)
Study 287	89.9% (132/147)	-	(84.9, 94.7)

* For uncontrolled studies, the 95% CI around the success rate is shown.

The treatment differences and 95% CIs for the clinical, bacteriological, and radiological response rates for the PP population at follow-up are illustrated in Figure 6, 7, and 8. In these 3 studies, the lower bound of the 95% CI for the treatment difference (gemifloxacin – comparator) was no less than the pre-defined non-inferiority limit of –10% for Studies 049 and –15% for Studies 011

and 185. The results of the ITT population confirmed the conclusion of the clinical PP population analyses.

Figure 6: Treatment Differences and 95% Confidence Intervals for Clinical Response Rates at Follow-Up: Individual Controlled CAP Studies (011, 012, 049, and 185) and Combined Analysis

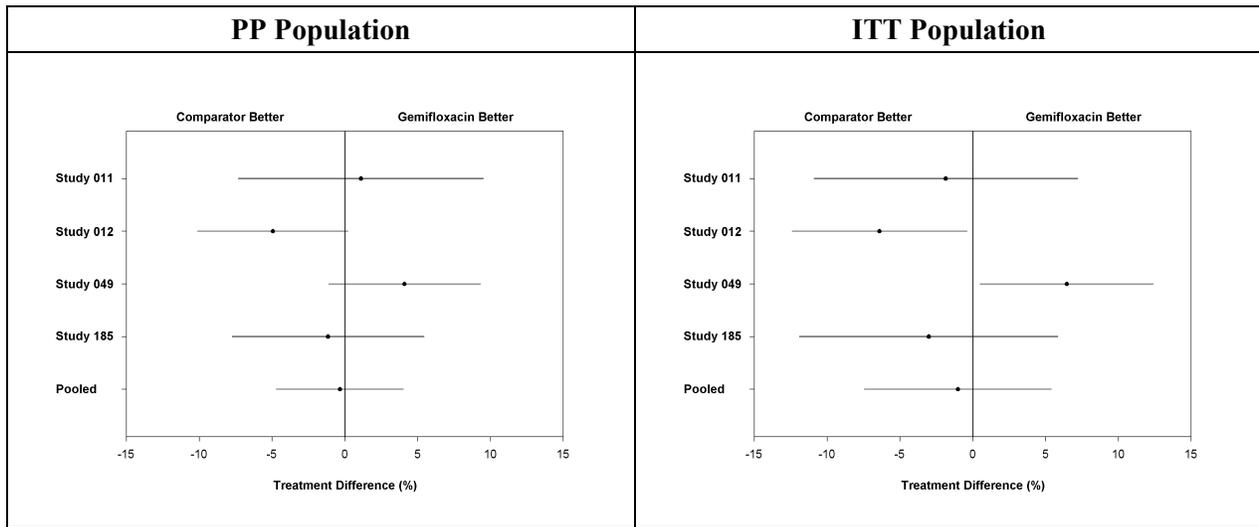


Figure 7: Treatment Differences and 95% Confidence Intervals for Bacteriological Response Rates at Follow-Up: Individual Controlled CAP Studies (011, 012, 049, and 185) and Combined Analysis

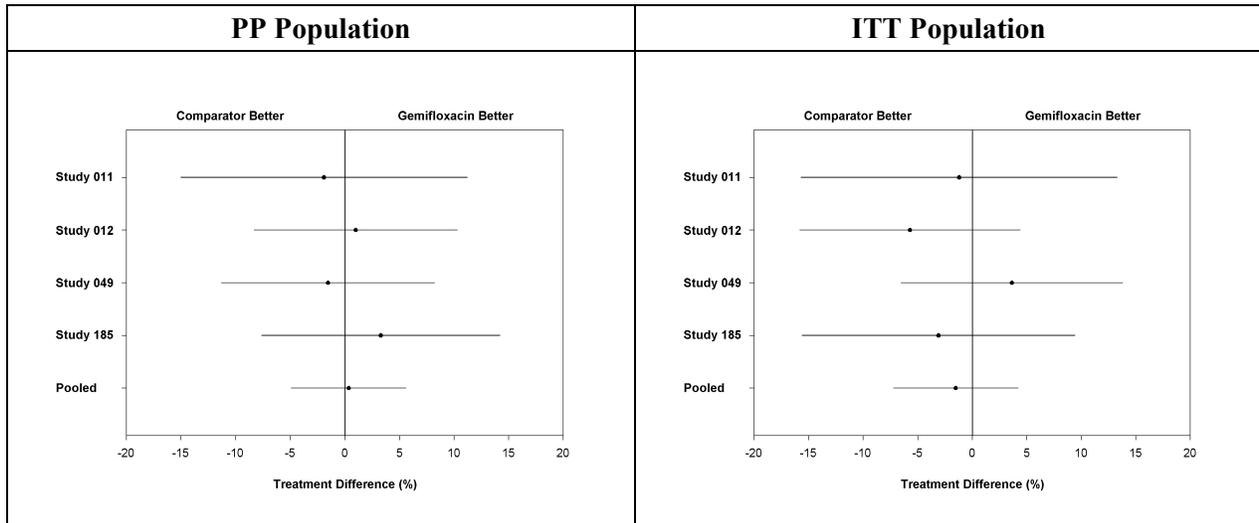
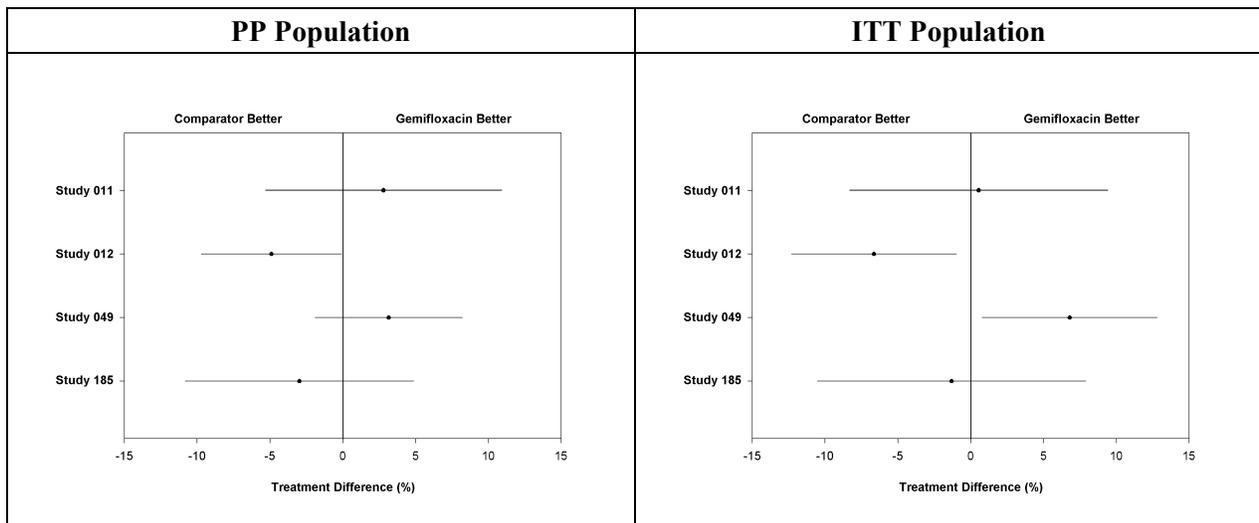


Figure 8: Treatment Differences and 95% Confidence Intervals for Radiological Response Rates at Follow-Up: Individual Controlled CAP Studies (011, 012, 049, and 185)



In Study 049 (ITT), the 95% CI for the treatment difference excluded zero, indicating that the clinical efficacy of gemifloxacin (87.5%, clinical success) was statistically significantly superior to trovafloxacin (81.1%, clinical success) for this population. In addition, although Study 049 was not designed to demonstrate non-inferiority for secondary endpoints, gemifloxacin was shown to be at least as good as trovafloxacin in terms of radiological response at follow-up and end of therapy in the clinical PP and ITT populations. In the gemifloxacin group, 87.6% (254/290) of patients were radiological successes at follow-up in the ITT population, compared with 80.8% (227/281) of patients in the trovafloxacin group. In this population, the 95% CI (0.8,12.8) for the treatment difference (gemifloxacin minus trovafloxacin) did not cross zero; hence the radiological efficacy of gemifloxacin was concluded to be statistically significantly superior to that of trovafloxacin.

In Study 012, the lower bound of the 95% CI for the treatment difference (-10.1%) fell just outside the limit to demonstrate non-inferiority (-10%) in the primary analysis (clinical PP population). For the ITT population, the 95% CI for the treatment difference did not include zero, suggesting that the clinical efficacy of gemifloxacin was significantly less than that of cefuroxime/clarithromycin. These results were influenced by the substantial proportion of missing data in Study 012 (12% of the gemifloxacin group and 7% of the comparator group were excluded from the PP population with a clinical outcome of unable to determine, and for the ITT population these patients with missing data were considered to be clinical failures). A different conclusion was obtained in a multiple imputation analysis, which provided an alternative methodology for handling missing data; the results of this analysis demonstrated a 95% CI for the treatment difference of (-7.6%, 2.2%).

A meta-analysis of the 4 controlled clinical studies further demonstrated the clinical effectiveness by both non-inferior clinical and bacteriological efficacy of oral gemifloxacin compared with combined comparators.

8.4.2 Subgroup Analysis

8.4.2.1 Efficacy by Demographic Characteristics

There was no evidence that age had an effect on the clinical response to gemifloxacin. The clinical success rates for gemifloxacin patients aged ≥ 65 -<75 years and ≥ 75 years were similar to the success rate for the younger age groups. There was no evidence of a difference in the clinical success rates between male and female CAP patients. The response rates for these subgroups were similar to the response rates observed in the total patient population.

8.4.2.2 Efficacy in Severe CAP, Hospitalized Patients, Bacteremia

High clinical and bacteriological success rates were demonstrated in patients with severe CAP (based on Fine Criteria [Fine et al. 1997]) (Table 36), hospitalized patients (Table 37), and patients with bacteremia at screening (Table 38).

Table 36: Rates of Clinical and Bacteriological Success at Follow-Up for Patients with Severe CAP: CAP Combined All Studies

	Gemifloxacin		Comparator	
	Success Rate % (n/N)	95% CI	Success Rate % (n/N)	95% CI
Clinical Response				
Clinical PP follow-up	93.4% (85/91)	88.3, 98.5	85.1% (57/67)	76.5, 93.6
Bacteriological Response				
Bacteriology PP follow-up	94.4% (34/36)	81.3, 99.3	76.7% (23/30)	57.7, 89.7

Note: Response rates for subgroup analyses are presented for the Combined All Studies dataset. No formal treatment comparisons between the gemifloxacin and comparator group are presented due to the inclusion of the uncontrolled studies.

Table 37: Rates of Clinical and Bacteriological Success at Follow-Up for Patients Hospitalized at Screening: CAP Combined All Studies

	Gemifloxacin		Comparator	
	Success Rate % (n/N)	95% CI	Success Rate % (n/N)	95% CI
Clinical Response				
Clinical PP follow-up	89.7% (496/553)	87.2, 92.2	89.5% (368/411)	86.6, 92.5
Bacteriological Response				
Bacteriology PP follow-up	88.5% (216/244)	84.5, 92.5	86.3% (139/161)	81.0, 91.6

Note: Response rates for subgroup analyses are presented for the Combined All Studies dataset. No formal treatment comparisons between the gemifloxacin and comparator group are presented due to the inclusion of the uncontrolled studies.

Table 38: Rates of Clinical and Bacteriological Success at Follow-Up for Patients who were Bacteremic at Screening: CAP Combined All Studies

	Gemifloxacin		Comparator	
	Success Rate % (n/N)	95% CI*	Success Rate % (n/N)	95% CI*
Clinical Response				
Clinical PP follow-up	89.6% (43/48)	77.3, 96.5	89.2% (33/37)	74.6, 96.9
Bacteriological Response				
Bacteriology PP follow-up	89.4% (42/47)	76.9, 96.4	88.9% (32/36)	73.9, 96.8

* 95% CI calculated using Exact Method

Note: Response rates for subgroup analyses are presented for the Combined All Studies dataset. No formal treatment comparisons between the gemifloxacin and comparator group are presented due to the inclusion of the uncontrolled studies.

8.4.2.3 Efficacy of a Planned Treatment Duration of 7 Days of Gemifloxacin

For pivotal Study 011 and supportive Studies 061 and 287 (interim data), the protocol specified a 7-day duration of treatment with gemifloxacin. In Studies 012 and 049, study medication could be extended to 14 days. In Study 185 treatment with gemifloxacin was for between 7 and 14 days. Response rates were investigated for patients categorized to subgroups based on 7 days or 14 days of gemifloxacin treatment in the CAP studies. Gemifloxacin treated patients in Study 185 were assigned to the 7-day treatment group if they received ≤ 7 days of treatment and to the 14-day subgroup if they received > 7 days of treatment. In Study 011, the treatment duration for all gemifloxacin patients was 7 days and for the comparator group it was 10 days. To enable comparisons, for the pooled analyses it was assumed that the planned treatment duration for both treatment groups in this study was 7 days

The interpretation of the response rates for these subgroups needs to consider the bias introduced due to the procedure for extending treatment duration. The decision to extend the treatment duration beyond 7 days was not taken at the time of randomization; patients needed to be responding to the drug at the on-therapy visit for treatment to be extended. Therefore the 14-day subgroup did not include any patients failing to respond at this visit. In contrast, all patients not responding at the on-therapy visit would have been withdrawn at this visit and included in the 7-day subgroup. The likely effect of this classification algorithm was to inflate the response rate for the 14-day subgroup and deflate the response rate for the 7-day treatment subgroup. The effect would be most pronounced in the ITT population. For this reason, when considering the results by duration of treatment, the evaluation of the efficacy of gemifloxacin should focus on the results for the 7-day and 14-day groups separately and should avoid comparison between these subgroups. Comparisons between gemifloxacin and comparator were not affected by the bias, as both groups were similarly affected.

In the CAP controlled studies, gemifloxacin for 7 days demonstrated high clinical and bacteriological success rates; 90.2% (431/478) of patients treated for 7 days had clinical success, and 87.4% (153/175) had bacteriological success (PP populations) (Table 39). For the PP populations, the clinical and bacteriological success rates for both the 7- and 14-day subgroups were high and consistent with the comparator rates for the same treatment duration

Table 39: Rates of Clinical and Bacteriological Success at Follow-Up by Planned Treatment Duration: CAP Combined Controlled Studies¹

	Success Rate		Treatment Difference % (95% CI)**
	Gemifloxacin	Comparator	
	% (n/N) 95% CI	% (n/N) 95% CI	
Clinical Response	N=697	N=698	
Clinical PP follow-up			
7 days*	90.2% (431/478)	90.7% (418/461)	0.2 (-6.5, 6.9)
14 days	91.3% (200/219)	92.0% (218/237)	-0.4 (-6.9, 6.1)
Bacteriology	N=280	N=274	
Bacteriology PP follow-up			
7 days*	87.4% (153/175)	90.7% (146/167)	21.3 (-13.6, 56.1)
14 days	91.4% (96/105)	90.7% (97/107)	-0.2 (-7.6, 7.2)

¹ Study Nos. 011, 012, 049, and 185

Notes: N = number of patients in the analysis population, n = number of patients who were a success, N = number of patients included in the subgroup.

* Includes all Study 011 patients although the comparator group received 10 days treatment.

** Treatment difference and 95% CI based on random effects meta-analysis performed for the controlled studies, using DerSimonian & Laird method, so the pooled treatment difference will not necessarily correspond to the difference in observed Gemifloxacin and 'All Comparators' response rates.

Gemifloxacin treatment for 7 days was effective across a broad spectrum of patients with CAP, including patients with severe CAP (based on Fine Criteria), hospitalized patients, and patients with bacteremia. The key findings from the 7-day subgroup analyses were as follows.

In Study 011, where all gemifloxacin patients planned to receive 7 days treatment, gemifloxacin was equivalent to comparator in terms of clinical success for mild, moderate and severe forms of CAP. Approximately 63% of patients with severe CAP in all studies combined were categorized as receiving up to 7 days of treatment. The response to 7 days of gemifloxacin treatment in patients with severe CAP was high and similar to that in the corresponding subgroups for the combined comparator group (Table 40).

The majority (77%) of hospitalized patients received 7 days of gemifloxacin treatment. The response to 7 days of gemifloxacin treatment in hospitalized patients was high and similar to that in the corresponding subgroups for the combined comparator group (Table 41).

Approximately 52% of patients with bacteremia at screening received gemifloxacin treatment for up to 7 days. In bacteremic patients, clinical and bacteriological success rates were similar between 7 days of gemifloxacin treatment and 7 days of comparator treatment (Table 42).

Table 40: Rates of Clinical and Bacteriological Success at Follow-Up for Patients with Severe CAP by Planned Duration of Treatment: CAP Combined All Studies¹

	Gemifloxacin		Comparator	
	Success Rate % (n/N)	95% CI	Success Rate % (n/N)	95% CI
Clinical PP	N=91		N=67	
7 days*	94.7% (54/57)	85.4, 98.9	86.5% (32/37)	71.2, 95.3
14 days	91.2% (31/34)	76.3, 98.1	83.3% (25/30)	65.3, 94.2
Bacteriology PP	N=36		N=30	
7 days*	95.2% (20/21)	76.2, 99.9	66.7% (8/12)	34.9, 88.9
14 days	93.3% (14/15)	68.1, 99.8	83.3% (15/18)	58.6, 96.2

* Includes all Study 011 patients although the comparator group received 10 days of treatment.

¹ Study Nos. 011, 012, 049, 185, 061, and 287

Table 41: Rates of Clinical and Bacteriological Success at Follow-Up for Hospitalized Patients by Planned Duration of Treatment: CAP Combined All Studies¹

	Gemifloxacin		Comparator	
	Success Rate % (n/N)	95% CI	Success Rate % (n/N)	95% CI
Clinical PP	N=553		N=411	
7 days	89.4% (378/423)	86.0, 92.1	87.6% (226/258)	82.9, 91.3
14 days	90.8% (118/130)	84.4, 95.1	92.8% (142/153)	87.5, 96.3
Bacteriology PP	N=244		N=161	
7 days	87.1% (149/171)	81.2, 91.7	84.9% (73/86)	75.5, 91.6
14 days	91.8% (67/73)	83.0, 97.0	88.0% (66/75)	78.4, 94.3

* Includes all Study 011 patients although the comparator group received 10 days of treatment.

¹ Study Nos. 011, 012, 049, 185, 061, and 287

Table 42: Rates of Clinical and Bacteriological Success at Follow-Up for Patients with Bacteremia by Planned Duration of Treatment: CAP Combined All Studies¹

	Gemifloxacin		Comparator	
	Success Rate % (n/N)	95% CI ⁺	Success Rate % (n/N)	95% CI ^{**}
Clinical PP	N=48		N=37	
7 days*	84.0% (21/25)	63.9, 95.3	82.6% (19/23)	61.2, 94.8
14 days	95.7% (22/23)	78.1, 99.9	100.0% (14/14)	76.8, 100.0
Bacteriology PP	N=62		N=52	
7 days*	84.0% (21/25)	63.9, 95.3	86.4% (19/22)	65.1, 97.0
14 days	95.5% (21/22)	77.2, 99.9	92.9% (13/14)	66.1, 99.8

¹ Study Nos. 011, 012, 049, 185, 061, and 287

* Includes all Study 011 patients although the comparator group received 10 days of treatment.

+95% CI calculated using Exact Method.

Note: Response rates for subgroup analyses are presented for the Combined All Studies dataset. No formal treatment comparisons between the gemifloxacin and comparator group are presented due to the inclusion of the uncontrolled studies.

8.4.3 Eradication of Key Pathogens in Gemifloxacin CAP Studies

High eradication rates of the key pathogens associated with CAP were demonstrated, namely against *S. pneumoniae* (including penicillin-resistant strains, macrolide-resistant strains, and cefuroxime-resistant strains); *H. influenzae*, *S. aureus*, *H. parainfluenzae* and *M. catarrhalis* (including β -lactamase-producing strains); *K. pneumoniae*; *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*.

As anticipated, the gemifloxacin MICs were low for all strains of *S. pneumoniae* (including penicillin-resistant strains, macrolide-resistant strains, and cefuroxime-resistant strains) with consistently high rates of clinical cure and bacterial eradication across the MIC spectrum (Table 43).

Table 43: Bacteriological Eradication and Clinical Cure Rates for *S. Pneumoniae* Pathogens by Gemifloxacin MIC - CAP

Gemifloxacin MIC (µg/mL)	ITT Population		PP Population	
	Bacteriological Eradication n/N (%)	Clinical Cure n/N (%)	Bacteriological Eradication n/N (%)	Clinical Cure n/N (%)
0.002	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)
0.008	26/29 (89.7)	26/29 (89.7)	23/25 (92)	23/25 (92)
0.015	69/85 (81.2)	69/85 (81.2)	58/64 (90.6)	58/64 (90.6)
0.03	29/36 (80.6)	29/36 (80.6)	25/27 (92.6)	25/27 (92.6)
0.06	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
Not available	7/12 (58)	7/12 (58)	6/7 (86)	6/7 (86)
Total	134/165 (81.2)	134/165 (81.2)	115/126 (91.3)	115/126 (91.3)

With 7 days of gemifloxacin treatment, the percent of strains eradicated were as follows: All pathogens - 86.9% (332/382 strains), *S. pneumoniae* - 89.9% (89/99 strains), *H. influenzae* - 87.8% (43/49 strains), *S. aureus* - 78.9% (15/19 strains), *H. parainfluenzae* - 66.7% (6/9 strains), *M. catarrhalis* - 100.0% (11/11 strains), *K. pneumoniae* - 94.1% (16/17 strains), *M. pneumoniae* - 85.2% (69/81 strains), *C. pneumonia* - 96.9% (31/32 strains), and *L. pneumophila* - 71.4% (10/14 strains).

8.4.4 Gemifloxacin in CAP Due to PRSP

Gemifloxacin was highly effective in the treatment of CAP due to PRSP (penicillin MIC of ≥ 2 µg/mL). Of 12 patients with PRSP in the PP population, all achieved clinical and bacteriological successes at follow-up (100% success rate, 95% CI: 73.5%, 100%). All but one of the 12 PRSP patients received treatment for 7 days. PRSP isolated from 10 of these 12 (83%) PP successes were also resistant to macrolides. Within the ITT population there were 14 patients with PRSP-related infections, of which 13 were clinical successes at follow-up. Three patients within the ITT population were bacteremic with PRSP, and all were successfully treated at follow-up. Two of these bacteremic patients were included in the PP population, one of whom received therapy for greater than 7 days.

From the second interim data lock of Study 287 (performed after the NDA resubmission was provided to the FDA and not yet reviewed by the Division) an additional 4 patients with PRSP were identified. Three of these 4 subjects were considered to have achieved clinical success (ITT population).

8.4.5 Efficacy of Gemifloxacin Treatment in CAP due to Macrolide Resistant *S. Pneumoniae*

Gemifloxacin was highly effective in the treatment of CAP due to MRSP (tested against clarithromycin or erythromycin and clarithromycin, MIC of ≥ 1 $\mu\text{g}/\text{mL}$). Within the PP population there were 22/25 (88.0%, 95% CI: 68.8, 97.3) patients with macrolide-resistant isolates who were treated with gemifloxacin and achieved clinical and bacteriologic success at follow-up. For patients treated with gemifloxacin for 7 days, 19/22 (86.4%, 95% CI: 65.1, 97.0) patients achieved clinical and bacteriologic success.

From the second interim data lock of Study 287 (performed after the NDA resubmission was provided to the FDA and not yet reviewed by the Division) an additional 10 patients with MRSP were identified. Six of these 10 subjects were considered to have achieved clinical success (ITT population).

8.4.6 Efficacy of Gemifloxacin Treatment in CAP due to Cefuroxime-Resistant *S. Pneumoniae*

Gemifloxacin was highly effective in the treatment of CAP due to CRSP. For patients with cefuroxime-resistant *S. pneumoniae*, 94.7% (18/19) of PP patients achieved both clinical and bacteriological successes at follow-up; 17 of 18 (94.4%) in the gemifloxacin PP group were treated for 7 days.

From the second interim data lock of Study 287 (performed after the NDA resubmission was provided to the FDA and not yet reviewed by the Division) an additional 5 patients with CRSP were identified. Four of these 5 subjects were considered to have achieved clinical success (ITT population).

8.4.7 Efficacy of Gemifloxacin in CAP Due to *S. Pneumoniae* Resistant to Ciprofloxacin

High response and eradication rates were maintained against *S. pneumoniae* isolates with MICs against ciprofloxacin ranging from 0.25 to 4 $\mu\text{g}/\text{mL}$. In the combined gemifloxacin group, 22/24 isolates of *S. pneumoniae* with an MIC to ciprofloxacin of 2 $\mu\text{g}/\text{mL}$ were eradicated and 4/4 isolates of *S. pneumoniae* with an MIC against ciprofloxacin of 4 $\mu\text{g}/\text{mL}$ were also successfully eradicated (all 4 isolates were from patients with a planned treatment duration of 7 days); the breakpoint defined as resistant by the product information sheet. For patients treated with *S. pneumoniae* resistant to ciprofloxacin, the clinical and bacteriological success rate associated with these isolates was 100% for both the Bacteriology PP and Bacteriology ITT populations.

8.5 Conclusions in CAP

Overall, gemifloxacin is effective in treating CAP both inside and outside the hospital.

The results of the CAP clinical program demonstrate that gemifloxacin for 7 days is an effective antibacterial treatment for CAP. Gemifloxacin for 7 days can provide appropriate coverage when used as an empirical therapy for the treatment of CAP in the prevailing environment of resistance to traditional antibacterial agents.

High clinical and bacteriological success rates are demonstrated with 7 days of gemifloxacin treatment. Radiological responses support the efficacy of oral gemifloxacin for treatment of patients with CAP.

Oral gemifloxacin is as effective as an IV to oral cephalosporin for treating hospitalized CAP patients. Additionally, gemifloxacin shows statistical superiority (ITT) in a head to head trial against another very potent quinolone, trovafloxacin.

Oral gemifloxacin is highly efficacious in patient subgroups that were representative of the disease spectrum including patients with severe CAP and hospitalized patients. High success rates occur in these patient subgroups when gemifloxacin is administered for 7 days. In patients with bacteremia at screening, clinical and bacteriological success rates are comparable between 7 days of gemifloxacin treatment and 7 days of comparator treatment.

High eradication rates are demonstrated with 7 days of gemifloxacin treatment for key pathogens associated with CAP including *S. pneumoniae* (including penicillin-resistant, macrolide-resistant, ciprofloxacin-resistant, and cefuroxime-resistant strains), *H. influenzae*, *S. aureus*, *H. parainfluenzae*, *M. catarrhalis* (including β -lactamase-producing strains), *K. pneumoniae*, and atypical organisms including *M. pneumoniae* and *C. pneumoniae*.

9. REVIEW OF SAFETY

9.1 Demographics

The safety profile of gemifloxacin is based on data, which comprises 6775 patients in Phase II and Phase III studies who received gemifloxacin 320 mg PO orally and 5248 patients who received comparators. This population excludes patients who received gemifloxacin at doses other than 320 mg PO.

The demographic characteristics of the safety populations are summarized in Table 44.

Table 44: Demographic Characteristics in Clinical Studies (Gemifloxacin 320 mg versus All Comparators)

Demographic Characteristics	Treatment Group			
	Gemifloxacin 320 mg PO		All Comparators	
	N=6775		N=5248	
	n	(%)	N	(%)
Age (years)				
≥16 - <18	22	(0.3)	8	(0.2)
≥18 - <40	1689	(24.9)	1029	(19.6)
≥40 - <65	3000	(44.3)	2398	(45.7)
≥65 - <75	1285	(19.0)	1126	(21.5)
≥75	779	(11.5)	687	(13.1)
Mean (SD)	52.8 (17.98)		55.1 (17.19)	
Median	54		57	
Range	16-97		16-99	
Gender				
Male	3278	(48.4)	2511	(47.8)
Female	3497	(51.6)	2737	(52.2)
Race				
White	5871	(86.7)	4825	(91.9)
Black	298	(4.4)	192	(3.7)
Oriental	227	(3.4)	43	(0.8)
Other	379	(5.6)	188	(3.6)
Indication				
AECB	2847	(42.0)	2591	(49.4)
CAP	1160	(17.1)	926	(17.6)

9.2 Patient Adverse Event Profile

9.2.1 Overall

The overall adverse event (AE) rate and the rates of specific AEs were similar in the gemifloxacin 320 mg PO group and the all-comparators group, except that the gemifloxacin group had a higher incidence of rash (Table 45).

A very small number of patients ($\leq 0.6\%$ out of 5248 gemifloxacin-treated patients, 4154 comparator treated patients) presented with hypoglycemia [serum glucose reduced by 25% of normal range low] at screening. Although infrequently observed at screening (0.2%), a comparable percentage of gemifloxacin 320 mg treated and comparator treated patients were hypoglycemic at either the on therapy (0.3% versus 0.6%) or at the end of therapy visit (0.4% versus 0.3%). The incidence of hypoglycemia among 640 mg gemifloxacin treated and

comparator treated patients remained unchanged between screening (0.6% versus 0.2%) and on therapy (0.6% versus 0.6%) and decreased somewhat by the end of therapy visit (0.3% versus 0.0%). Hypoglycemia was not reported for any patient receiving oral hypoglycemic agents or insulin comitant with gemifloxacin 320 or 640 mg.

Table 45: Number (%) of Patients With the Most Frequently Occurring ($\geq 1\%$) Adverse Experiences in Either Treatment Group During the Interval On-Therapy Plus 30 Days Post-Therapy

Preferred Term	Treatment Group			
	Gemifloxacin 320 mg PO		All Comparators	
	N=6775		N=5248	
	n	(%)	N	(%)
Patients with at least one AE	3029	(44.7)	2492	(47.5)
Diarrhea	343	(5.1)	325	(6.2)
Headache	304	(4.5)	273	(5.2)
Nausea	265	(3.9)	237	(4.5)
Rash*	241	(3.6)	59	(1.1)
Abdominal Pain	157	(2.3)	116	(2.2)
Vomiting	123	(1.8)	106	(2.0)
Dizziness	117	(1.7)	134	(2.6)
Rhinitis	105	(1.5)	74	(1.4)
Insomnia	100	(1.5)	92	(1.8)
Hyperglycemia	98	(1.4)	70	(1.3)
Injury	96	(1.4)	60	(1.1)
Back Pain	93	(1.4)	75	(1.4)
Creatine Phosphokinase Increased	90	(1.3)	64	(1.2)
Sinusitis	84	(1.2)	69	(1.3)
Constipation	73	(1.1)	62	(1.2)
Flatulence	69	(1.0)	40	(0.8)
Myalgia	67	(1.0)	45	(0.9)
SGPT Increased	67	(1.0)	49	(0.9)
Dyspepsia	66	(1.0)	74	(1.4)
Fatigue	66	(1.0)	57	(1.1)
Bronchitis	64	(0.9)	75	(1.4)
Upper Respiratory Tract Infection	58	(0.9)	67	(1.3)
Pharyngitis	57	(0.8)	73	(1.4)
Moniliasis Genital	48	(0.7)	57	(1.1)
Mouth Dry	33	(0.5)	51	(1.0)
Taste Perversion	21	(0.3)	108	(2.1)

*Rash includes the preferred terms rash, rash erythematous, rash maculo-papular and rash pustular.

Proportionally, slightly fewer patients in the gemifloxacin 320 mg PO group than in the all-comparators group had at least one AE of suspected or probable relationship to study medication. The gemifloxacin group showed a higher percentage of patients with rash and a lower percentage with taste perversion of suspected or probable relationship than the comparator group. Unlike other members of the quinolone class, gemifloxacin has a low potential for CNS side effects.

9.2.2 Serious Adverse Events (SAEs)

The overall incidence of SAEs was low in both treatment groups, 3.6% among patients treated with gemifloxacin 320 mg PO and 4.3% among patients in the all-comparators group. The proportion of patients having SAEs with a suspected or probable relationship to study medication was less than 1% in both the gemifloxacin 320 mg PO group and the all-comparators group.

9.2.3 Withdrawals Due to AEs

The overall incidence of adverse events leading to withdrawal in the gemifloxacin 320 mg treatment group was equal to or lower than the incidence in the all-comparators treatment group, 3.9% (264/6775) vs. 4.3% (226/5248), respectively. Similarly, low percentages of patients in the gemifloxacin 320 mg PO and all-comparators groups were withdrawn for AEs of suspected or probable relationship to study medication during the interval on-therapy plus 30 days post-therapy, 2.2% (152/6775) vs. 2.1% (109/5248), respectively.

9.2.4 Deaths

The death rate in the gemifloxacin 320 mg PO treatment group was very low and similar to that in the all-comparators group, 0.5% (33/6775) vs. 0.6% (30/5248), respectively.

9.3 Rash

Reports of photosensitivity reaction with gemifloxacin were rare. A total of 3/7659 patients in the all exposed gemifloxacin group and 2/5549 in the all comparator group reported photosensitivity reactions in clinical studies. All reports were considered by the investigator to be of mild or moderate intensity and no patients were withdrawn due to a photosensitivity reaction.

Patients taking gemifloxacin 320 mg PO had higher incidences of rash and rash leading to withdrawal than those taking comparators. A significant difference in the incidence of rash was observed between the gemifloxacin 320 mg PO group and the all-comparators group, 3.6% (241/6775) and 1.1% (59/5248) patients, respectively ($p < 0.001$) (Table 46).

Table 46: Incidence of Adverse Experiences of Rash for Both Treatment Groups

Type of AE	Treatment Group			
	Gemifloxacin 320mg PO N=6775		All Comparators N=5248	
	N	(%)	n	(%)
Rash*	241	(3.6) ⁺	59	(1.1)
SAE of rash*	7	(0.1)	1	(<0.1)
Rash* leading to withdrawal	64	(0.9)	15	(0.3)

*Rash includes the preferred terms rash, rash erythematous, rash maculo-papular, and rash pustular.

SAEs of rash were rare in both treatment groups, occurring in 7/6775 (0.1%) patients in the gemifloxacin 320 mg PO group and 1/5248 (<0.1%) patient in the all-comparators group. The specific reasons for the rash SAEs reported on gemifloxacin are presented in Table 47. The first four were classified as SAEs because the patients were hospitalized. This represents the different standard of care in Eastern Europe. These patients would have been treated for rash as outpatients in North American or Western Europe. In the Canadian case the patient was afebrile and the rash cleared in 2 days. The Dutch case had a rash that began quickly and was of long duration, but the patient was not admitted to hospital. The U.S. case was more complex and may have represented a cutaneous reaction to mycoplasma infection. It does not fit either a serum sickness vasculitis or a serum sickness-like reaction. However, with rash, fever and joint involvement it can be considered a possible serum sickness-like reaction. Of the 7 patients with SAEs to rash only two are of possible concern (<0.03%); however, both cases had multiple possible etiologies.

Table 47: Reason for Gemifloxacin Rash SAEs

Patient Description	Center Location	Reason for SAE	Comments/Outcome
18 yr old male, 7 days dosing, ABS	Hungary	Hospitalization	Paul-Bunnell test positive “Rash probably associated with underlying mononucleosis and drug”
24 yr old female, 8 days dosing, ABS	Poland	Hospitalization	Hospitalization for treatment with steroid and anti-histamine. Recovered by day three.
52 yr old female, 9 days dosing, ABS	Poland	Hospitalization	Mild rash. No medical reason for hospitalization but patient required reassurance.
60 yr old female, 8 days after 1 st dose, UTI	Poland	Hospitalization	Rxed with steroid, antihistamine and calcium. Recovered within 7 days.
87 yr old male, 7 days dosing, CAP	Canada	Investigator judgment	Patient noted to have rash 48 hours post therapy. Asymptomatic, afebrile, reported to be fading in 2 days without intervention.
72 yr old male, 2 days dosing, AEBC	Netherlands	Investigator judgment	Allergic to gold and penicillin. Receiving 8 co- medications. Maculopapular, maculoconfluent rash on body and limbs with severe itching. “Treated with antihistamine. Resolving at day 18”.
42 yr old female, 4 days dosing, ABS	U.S.	Investigator judgment	Serum sickness onset 13 days after last dose, generalized maculopapular rash with few vesicles, fever, chills, joint pains, cough, CXR infiltrate in RLL serological diagnosis of acute mycoplasma pneumoniae infection. Largely resolved after 15 days

ABS = acute bacterial sinusitis

Rash as a cause of withdrawal was very low in both treatment groups, occurring in 64/6775 (0.9%) patients in the gemifloxacin 320 mg PO group and 15/5248 (0.3%) patients in the all-comparators group, respectively. Although infrequent, this difference was statistically significant (p<0.001).

There were 6 reported cases of facial edema in the clinical trials (Table 48). None appeared to represent angioedema and did not represent even urticaria. Only one used any intervention (Allegra), and most could continue gemifloxacin. The reactions were mild to moderate. None of the episodes of facial edema were considered by the investigator to be serious.

Table 48: Episodes of Facial Edema in Clinical Trials

PID	Verbatim Text	Maximum Intensity	Onset	Rash	Treatment	Outcome
053.037.37005	Facial edema	Moderate	On therapy	Yes	Drug Stopped / Allegra Rx	Resolved in 5 days
067.051.17881	Swollen face	Mild	On therapy	Yes	None	Resolved in 1 day
053.037.37001	Facial edema	Moderate	3 weeks post-therapy	No	None	Resolved in 2 days
053.037.52009	Facial swelling	Moderate	3 weeks post-therapy	No	None	Resolved in 1 day
112.722.35618	Puffy face	Mild	4 months post-therapy	No	None	Resolved in 2 days
212.164.55322	Swelling of the eyelids	Moderate	On therapy	No	None	Resolved in 5 days

Having observed that the rash rate was increased in patients taking gemifloxacin, multivariate analysis was conducted to determine risk factors for rash. Relevant risk factors identified for rash included patients with longer treatment duration, patients <40 years of age, and female patients. In female patients ≥ 40 years or age, the use of hormone replacement therapy (HRT) was also associated with the occurrence of rash but not for drug-related rash. In female patients <40 years or age, the use of oral contraceptives (OCs) was not associated with rash.

9.3.1 Rash by Duration of Treatment

The incidence of rash increased with longer gemifloxacin treatment durations, the lowest incidence being the 5-day subgroup (1.2%) and the highest incidence being the 14-day subgroup (7.4%) (Table 49). This trend was also observed in the all-comparators group, although it was somewhat less marked.

Table 49: Number (%) of Patients with Rash by Duration of Treatment

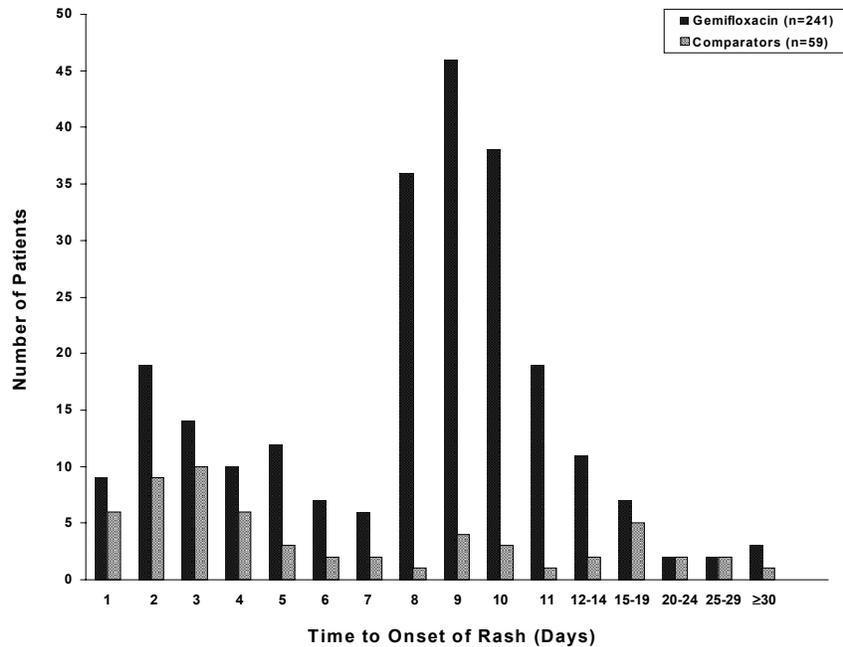
Day	Treatment Group			
	Gemifloxacin 320 mg PO		All Comparators	
	N=6775		N=5248	
	n	(%)	n	(%)
3	14/501	(2.8)	2/444	(0.5)
5	37/2991	(1.2)	3/334	(0.9)
7	112/2113	(5.3)	24/2234	(1.1)
10	55/858	(6.4)	21/1919	(1.1)
14	23/312	(7.4)	9/317	(2.9)

9.3.2 Time to Onset of Rash

The median time to onset of the rash from the start of study medication was 9.0 days for the gemifloxacin group and 4.0 days for the all-comparators group (Figure 9).

The distribution of values for time to onset of rash showed clustering of values around the medians, but otherwise no clear patterns were evident.

Figure 9: Time to Onset of Rash from Start of Study Medication

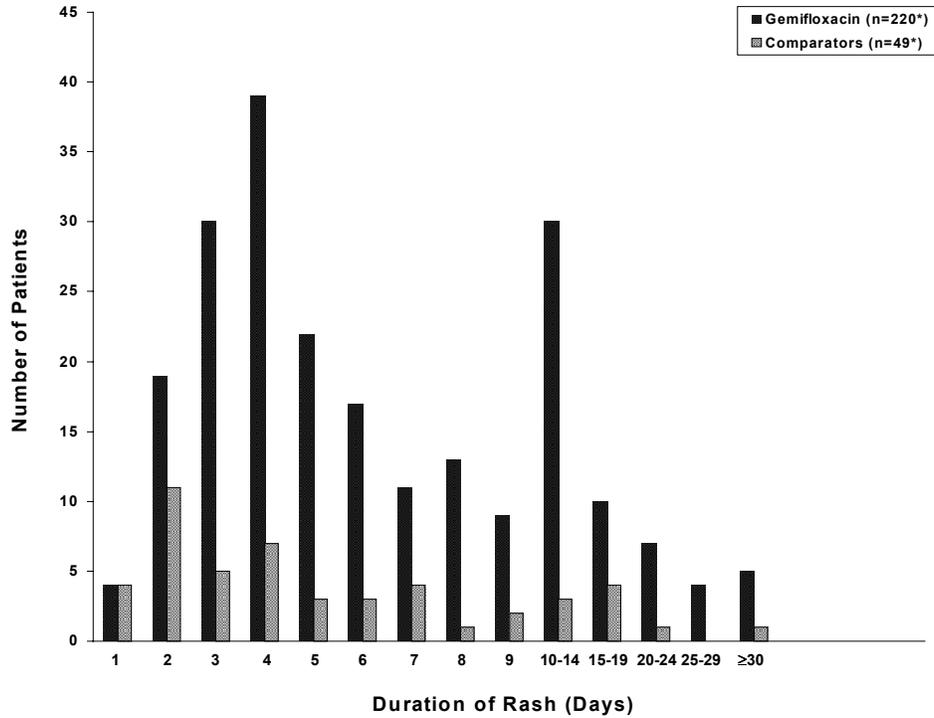


9.3.3 Duration of Rash

The median duration of the rash for the gemifloxacin group was 5.0 days, compared with 4.0 days for the all-comparators group.

The overall distribution of values for duration of rash was similar in the 2 treatment groups (Figure 10).

Figure 10: Duration of Rash



*Duration unknown in 21 gemifloxacin and 10 comparator patients

9.3.4 Severity of Rash

In both the gemifloxacin group and the all-comparators group, most rashes were of mild or moderate intensity, 86.6% and 93.4%, respectively. The frequency of severe rashes was low in both treatment groups, 13.4% of patients in the gemifloxacin group and 6.6% of patients in the all-comparators group.

The percentage of patients with severe rash did not increase with increasing duration of exposure to gemifloxacin (Table 50).

Table 50: Maximum Severity of Rash By Duration of Exposure

Extent of Exposure	Time Interval*									
	0-3 days		4-5 days		6-7 days		8-10 days		≥11 days	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gemifloxacin 320mg PO										
Mild	16	(61.5)	22	(57.9)	50	(48.1)	21	(37.5)	10	(58.8)
Moderate	6	(23.1)	15	(39.5)	35	(33.7)	28	(50.0)	5	(29.4)
Severe	4	(15.4)	1	(2.6)	19	(18.3)	7	(12.5)	2	(11.8)
Total⁺	26	(100)	38	(100)	104	(100)	56	(100)	17	(100)

* Includes rash AEs occurring on-therapy plus 30 days post-therapy

+Total number of patients with rash during the specified interval

Note: Day 0 is Day 1 of study medication

9.3.5 Rash by Gender

The frequency of rash was higher for both males and females in the gemifloxacin group than in the all-comparators group, 2.4% (78/3278) vs. 0.8% (20/2411) and 4.7% (163/3497) vs. 1.4% (39/2737), respectively. The frequency of rash was higher in females than in males in both the gemifloxacin and the all-comparators treatment groups.

9.3.6 Rash by Age, Gender, and Planned Treatment Duration

Table 51 presents the occurrence of rash according to age and gender, by planned treatment duration for the combined population.

Table 51: Number (%) of Patients with Rash by Age and Gender According to Planned Treatment Duration

Duration of Treatment	Gemifloxacin 320 mg PO N=6775					All Comparators N=5248				
	3 Days	5 Days	7 Days	10 Days	14 Days	3 Days	5 Days	7 Days	10 Days	14 Days
Gender/ Age (yrs)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Both, <40	10/334 (3.0)	9/460 (2.0)	59/642 (9.2)	27/205 (13.2)	10/70 (14.3)	1/287 (0.3)	0/1	3/156 (1.9)	9/523 (1.7)	0/70
Both, ≥40	4/167 (2.4)	28/2531 (1.1)	53/1471 (3.6)	28/653 (4.3)	13/242 (5.4)	1/157 (0.6)	3/333 (0.9)	21/2078 (1.0)	12/1396 (0.9)	9/247 (3.6)
All Males	0/71	13/1549 (0.8)	43/1094 (3.9)	16/419 (3.8)	6/155 (3.9)	0/0	2/202 (1.0)	8/1157 (0.7)	6/967 (0.6)	4/185 (2.2)
Males <40	0/69	4/218 (1.8)	20/318 (6.3)	7/74 (9.5)	3/39 (7.7)	0/0	0/1	2/82 (2.4)	3/211 (1.4)	0/46
Males ≥40	0/2	9/1321 (0.7)	23/776 (3.0)	9/345 (2.6)	3/116 (2.6)	0/0	2/201 (1.0)	6/1075 (0.6)	3/756 (0.4)	4/139 (2.9)
All Females	14/430 (3.3)	24/1452 (1.7)	69/1019 (6.8)	39/439 (8.9)	17/157 (10.8)	2/444 (0.5)	1/132 (0.8)	16/1077 (1.5)	15/952 (1.6)	5/132 (3.8)
Females <40	10/265 (3.8)	5/242 (2.1)	39/324 (12.0)	20/131 (15.3)	7/31 (22.6)	1/287 (0.3)	0/0	1/74 (1.4)	6/312 (1.9)	0/24
Females ≥40	4/165 (2.4)	19/1210 (1.6)	30/695 (4.3)	19/308 (6.2)	10/126 (7.9)	1/157 (0.6)	1/132 (0.8)	15/1003 (1.5)	9/640 (1.4)	5/108 (4.6)

9.3.7 Rash by Oral Contraceptive Use or Hormone Replacement Therapy

The incidence of rash by OC use or HRT for each treatment group was assessed in female patients (Table 52 and 53, respectively). The frequency of rash was consistently higher in the gemifloxacin 320 mg PO group compared with the all-comparators group for both the OC use, 8.8% (39/444) vs. 1.3% (4/304), respectively, and HRT, 5.9% (26/442) vs. 1.0% (4/401), respectively, subgroups.

For female patients in the gemifloxacin group, the incidence of rash was higher in the OC use subgroup, 8.8% (39/444) vs. the non OC use subgroup, 4.1% (124/3053), and was also higher in the HRT subgroup, 5.9% (26/442), vs. the non HRT subgroup, 4.5% (137/3055). This trend was not noted in the all-comparators group.

Table 52: Number (%) of Female Patients with Rash by Oral Contraceptive Use

	Treatment Group							
	Gemifloxacin 320 mg PO N=3497				All Comparators N=2737			
	OC Use				OC Use			
	YES		NO		YES		NO	
	n	%	n	%	n	%	N	%
Female Patients <40 yrs	n=382		n=611		n=264		n=433	
Rash	33	(8.6)	48	(7.9)	4	(1.5)	4	(0.9)
Female Patients ≥40 yrs	n=62		n=2442		n=40		n=2000	
Rash	6	(9.7)	76	(3.1)	0		31	(1.6)
All Female Patients	n=444		n=3053		n=304		n=2433	
Rash	39	(8.8)	124	(4.1)	4	(1.3)	35	(1.4)

Table 53: Number (%) of Female Patients with Rash by HRT Use

	Treatment Group							
	Gemifloxacin 320 mg PO N=3497				All Comparators N=2737			
	HRT Use				HRT Use			
	YES		NO		YES		NO	
	n	%	n	%	n	%	n	%
Female Patients <40yrs	n=16		n=977		n=9		n=688	
Rash	2	(12.5)	79	(8.1)	0	(0)	8	(1.2)
Female Patients ≥40yrs	n=426		n=2078		n=392		n=1648	
Rash	24	(5.6)	58	(2.8)	4	(1.0)	27	(1.6)
All Female Patients	n=442		n=3055		n=401		n=2336	
Rash	26	(5.9)	137	(4.5)	4	(1.0)	35	(1.5)

9.3.8 Rash by Indication

The incidence of rash for each treatment indication (AECB, CAP) was assessed (Table 54 and 55, respectively). The frequency of rash was higher in the gemifloxacin 320 mg PO group compared to the all-comparators group for each therapeutic indication. In the combined CAP and AECB populations (all studies and all duration of gemifloxacin therapies from those studies excluding CAP Study 287), the rash rate was 2.5%, overall. Analyzing only those study subjects who received gemifloxacin for the proposed duration of treatment for AECB (5 days) and CAP (7 days) the rash rates were 1.2% and 4.0%, respectively.

Table 54: Patients with AECB with Rash On Therapy Plus 30 Days Post Therapy – Combined Population

Duration of Treatment	Gemifloxacin				Comparators			
	≤ 5 days		> 5 days		≤ 7 days		> 7 days	
	Total Pts.	n (%)	Total Pts.	n (%)	Total Pts.	n (%)	Total Pts.	n (%)
Both, all ages	2284	27 (1.2)	563	17 (3.0)	2522	21 (0.8)	69	0
Both, < 40 years	41	0	17	3 (17.6)	55	0	4	0
Both, ≥ 40 years	2243	27 (1.2)	546	14 (2.6)	2467	21 (0.9)	65	0
All Females	1062	16 (1.5)	233	10 (4.3)	1157	15 (1.3)	26	0
Females, < 40 years	22	0	12	2 (16.7)	32	0	2	0
Females, ≥ 40 years	1040	16 (1.5)	221	8 (3.6)	1125	15 (1.3)	24	0
All Males	1222	11 (0.9)	330	7 (2.1)	1365	6 (0.4)	43	0
Males, < 40 years	19	0	5	1 (20.0)	23	0	2	0
Males, ≥ 40 years	1203	11 (0.9)	325	6 (1.8)	1342	6 (0.4)	41	0

Table 55: Patients with CAP with Rash On Therapy Plus 30 Days Post Therapy – Combined Population

Duration of Treatment	Gemifloxacin				Comparators			
	≤ 7 days		> 7 days		≤ 7 days		> 7 days	
	Total Pts.	n (%)	Total Pts.	n (%)	Total Pts.	n (%)	Total Pts.	n (%)
Both, all ages	643	26 (4.0)	517	29 (5.6)	422	9 (2.1)	504	10 (2.0)
Both, < 40 years	189	13 (6.9)	127	11 (8.7)	139	4 (2.9)	129	0
Both, ≥ 40 years	454	13 (2.9)	390	18 (4.6)	283	5 (1.8)	375	10 (2.7)
All Females	302	13 (4.3)	237	21 (8.9)	179	4 (2.2)	211	6 (2.8)
Females, < 40 years	88	8 (9.1)	44	7 (15.9)	61	1 (1.6)	46	0
Females, ≥ 40 years	214	5 (2.3)	193	14 (7.3)	118	3 (2.5)	165	6 (3.6)
All Males	341	13 (3.8)	280	8 (2.9)	243	5 (2.1)	293	4 (1.4)
Males, < 40 years	101	5 (5.0)	83	4 (4.8)	78	3 (3.8)	83	0
Males, ≥ 40 years	240	8 (3.3)	197	4 (2.0)	165	2 (1.2)	210	4 (1.9)

9.3.9 Previous Gemifloxacin Exposure

In the All Exposed population (all patients who received at least one dose of gemifloxacin including doses other than 320 mg PO), the total number of patients who were known to be exposed to gemifloxacin prior to re-exposure with gemifloxacin was 41/7659 (0.5%). The cross-tabulation showed that of these patients who were previously exposed to gemifloxacin, no patient

reported a rash AE at either the first exposure or upon re-exposure. These findings suggest that previous exposure to gemifloxacin does not appear to be a risk factor for the development of rash although the patient number is small.

9.3.10 Previous Quinolone Exposure

The total number of patients who were known to be exposed to another fluoroquinolone at any time prior to starting treatment with gemifloxacin was 181/7659 (2.4%). The quinolones of prior exposure included ciprofloxacin (74 patients) levofloxacin (50 patients), ofloxacin (20 patients), norfloxacin (19 patients), trovafloxacin (9 patients), cinoxacin (5 patients), pipemidic acid (5 patients), grepafloxacin (3 patients), gatifloxacin (3 patients), sparfloxacin (2 patients), pefloxacin (1 patient), and moxifloxacin (1 patient). There were 13 patients that reported previous exposure to more than one quinolone, resulting in 195 previous quinolone exposures. A total of 84/181 (46.4%) of the patients with prior quinolone exposure had received another quinolone during the two weeks immediately prior to gemifloxacin treatment.

Of the 181 patients that were known to be previously exposed to a quinolone antibiotic, 3 (1.7%) patients developed a rash (2 mild, 1 moderate) during gemifloxacin administration. For two of the three patients, the medical history was notable for allergic disease. These findings suggest that previous exposure to quinolone antibiotics does not sensitize patients to develop a rash upon subsequent exposure to gemifloxacin treatment.

9.3.11 Subsequent Exposure to Another Quinolone

Patients receiving gemifloxacin who developed a rash AE during the on-therapy plus 30 day post-therapy and were known to be subsequently exposed to another quinolone antibiotic were identified. Of twelve patients identified, eleven were subsequent exposures and one patient was a concurrent quinolone exposure (Day 3) with the rash AE occurring on Day 12. Of the 11 patients who developed a previous rash AE with gemifloxacin treatment and who were known to be subsequently exposed to another quinolone after completion of gemifloxacin treatment, no patient developed rash upon exposure to subsequent quinolone antibiotics. Thirteen subsequent exposures occurred, as follows: exposure occurred at 10 days (1), 15 days (2), 17 days (1), 18 days (2), 25 days (1), 30 days (1), 34 days (2), 72 days (1), 114 days (1), 130 days (1) after the first dose of gemifloxacin. Two patients had two subsequent exposures.

These findings suggest that patients who developed a rash associated with gemifloxacin treatment are at lower risk for cross-sensitization to other quinolone antibiotics.

9.3.12 Systemic Signs in Association with Rash

The number of patients in the combined population that met the definition of systemic involvement and also developed a rash AE was determined. Systemic signs were defined in terms of the laboratory values assessment, as follows:

Eosinophils: one high F2-flag (laboratory value increased by >200% of baseline, where the baseline value is not 0), AND

Liver function tests: at least one high F2F3-flag at any visit (laboratory value increased from baseline by more than the pre-specified amount and is outside the extended normal range high) for at least one of the following:

Alkaline phosphatase, ALT, and aspartate aminotransferase (AST): value increased from baseline by 75% and is >200% of normal range high.

Total bilirubin: value increased from baseline by 50% and is >150% of normal range high.

Patients not meeting the above criteria were categorized as not having systemic involvement.

Thirty-eight of 6775 (0.56%) of patients treated with gemifloxacin met the above criteria; although a small sample size, only 2 of the 38 (5.3%) patients developed a rash. Both patients who developed a rash had a history of allergic disease, which was likely to be a predisposing factor for the development of rash and systemic signs. In comparison, 239 of 6737 (3.5%) patients who did not meet the above laboratory criteria also developed a rash. These findings suggested that gemifloxacin use in patients developing rash did not appear to be associated with an increased risk for systemic involvement.

The 2 patients who met the laboratory criteria summarized above and also had a rash AE are summarized as follows:

PID 013.059.02417: This 35-year-old white female (country Sweden) had a history of rhinoconjunctivitis (due to pollen) and presented with increased white blood cell level at baseline. The patient took gemifloxacin for 10 days. The patient developed a rash on Day 8 lasting for 5 days described as mild and probably related to gemifloxacin. The patient had the following laboratory values:

	SCR	OT	EOT	Reference Range
ALT	30	<i>112</i>	31	0-47 IU/L
AST	35	69	20	0-37 IU/L
ALK	97	151	74	40-135 IU/L
Total bilirubin	16.5	4.9	11.0	0-19.00 µmol/L
Monocytes	1.42	0.49	0.47	0-0.80 x 10 ⁹ /L
Lymphocytes	2.39	1.7	0.44	1.20-4.0 x 10 ⁹ /L
Eosinophils	0.02	0.10	0.04	0-0.50 x 10 ⁹ /L
Neutrophils	20.87	6.81	3.49	1.8-7.0 x 10 ⁹ /L
WBC	6.8	5.4	3.0	3.80-11.00 x 10 ⁹ /L

SCR = Screening; OT = On-Therapy; EOT = End of Therapy.

*Units are shown only in the reference range column.

Note: F2F3-flagged values are bolded and in italics.

PID 014.045.06541: This 30-year-old white female (country U.S.) had a history of asthma, hay fever, and oral contraceptive use and presented with pruritus, characterized by itchy skin at night, on Day 0 lasting 11 days and of suspected relationship to gemifloxacin. The patient took gemifloxacin for 10 days. The patient developed a rash on Day 10 lasting 1 day described as mild and of suspected relationship to gemifloxacin. The patient developed hay fever on Day 18 lasting 2 days and considered unrelated to gemifloxacin.

	SCR	OT	EOT	Reference Range
ALT	51	<i>139</i>	50	0-42 IU/L
AST	28	40	27	0-37 IU/L
ALK	72	83	98	20-125 IU/L
Total bilirubin	10.26	8.55	10.26	0-22.23 µmol/L
Monocytes	0.98	0.5	0.01	0.20-1.10 x 10 ⁹ /L
Lymphocytes	1.19	1.42	1.45	0.85-4.10 x 10 ⁹ /L
Eosinophils	0.11	0.28	0.32	0.05-0.55 x 10 ⁹ /L
Neutrophils	5.17	3.24	2.6	1.8-7.0 x 10 ⁹ /L
WBC	7.5	5.5	4.4	3.80-10.80 x 10 ⁹ /L

SCR = Screening; OT = On-Therapy; EOT = End of Therapy.

*Units are shown only in the reference range column.

Note: F2F3-flagged values are bolded and in italics.

Although from a technical perspective these two patients may have met the eosinophil count criteria to be classified as having rash in association with systemic signs, neither of these two patients met the standard definition for peripheral eosinophilia of >500 cells/mm³ at any time during or after therapy with gemifloxacin. Although both did develop mild liver function test

abnormalities these were noted early in their course with gemifloxacin (on therapy visit typically occurred on days 2-4 of treatment) and were already resolving by the end of therapy visit when the rash was just developing for both subjects.

9.3.13 Immune System Reactions in Association With Rash

A total of 7/6775 (0.1%) patients taking gemifloxacin 320 mg PO and 2/5248 (<0.1%) patients in the all-comparators group who reported rash also concurrently experienced fever, arthralgia, and/or lymphadenopathy. This included 2.9% (7/241) of patients in the gemifloxacin group and 3.4% (2/59) of patients in the all-comparators group reporting rash AEs.

A total of 52/6775 (0.8%) of gemifloxacin treated patients reported fever, and of these, 3 (5.8%) patients developed rash. Two patients developed a transient fever during treatment or shortly thereafter, with a moderate rash developing after the last treatment. The other patient developed a fever and rash more than 2 weeks after treatment.

A total of 45/6775 (0.7%) of gemifloxacin treated patients reported arthralgia, and of these, 3 (6.7%) patients developed rash. Additionally, a total of 4/6775 (<0.1%) of patients reported arthralgia and lymphadenopathy, and of these, 1 (25.0%) patient developed rash. There were 2 cases of arthralgia associated with rash in the all-comparators group.

In summary, the scope of the possible immune system reactions associated with rash included 7 cases of fever, arthralgia, and/or lymphadenopathy in patients receiving gemifloxacin 320 mg PO. Three patients had concurrent rash and fever, 3 patients had concurrent rash and arthralgia, and 1 patient had concurrent rash and arthralgia and lymphadenopathy. No patient had developed rash concurrently with lymphadenopathy alone. For the cases of fever, it preceded the development of the rash, and for the cases of arthralgia, it occurred subsequent to the occurrence of rash, except for 1 case. In general, patients taking gemifloxacin do not appear to be at a higher risk for further adverse events involving the lymphatic system or the articular system as a result of developing a rash.

9.4 Study 344

Having observed that the rash rate was increased in patients taking gemifloxacin, a special landmark clinical study, Study 344, was conducted to further characterize the gemifloxacin-associated rash. Specifically, Study 344 was designed to assess the following:

- The clinical and histological characteristics of gemifloxacin associated rash.

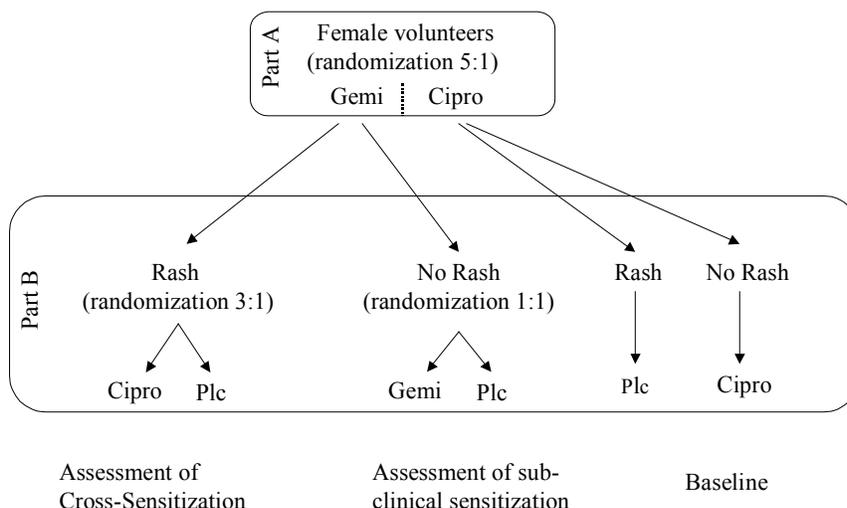
- The potential for cross-sensitization to other quinolones (as represented by ciprofloxacin) in subjects who experienced gemifloxacin-associated rash.
- The potential for sub-clinical sensitization in subjects not developing a rash on first exposure to gemifloxacin
- To explore the relationship between plasma levels of gemifloxacin and N-acetyl gemifloxacin and the incidence of rash.

Study 344 was intentionally designed with an enriched population considered to be at higher risk for development of rash treated for a longer duration than intended for CAP and AECB treatment, in order to elicit enough rashes to assess the possible immune basis, outcome of the rash, and to comprehensively characterize the rash. It therefore enrolled subjects most likely to develop a rash following exposure, namely female subjects aged <40 years, who were then exposed to 10 days of treatment, which was longer than the intended duration of treatment, 5 to 7 days, in order to maximize the incidence of rash. It is important to note that this population is not typical of the target population for gemifloxacin, namely patients with CAP and AECB, who are more often male, older than 40 years of age, and will be treated with 7 days or less of gemifloxacin.

9.4.1 Study Design

In order to maximize the occurrence of rash, the study exposed female subjects aged <40 years to 10 days of treatment with gemifloxacin. The study was performed in two parts, Part A and Part B (Figure 11). Both Part A and Part B were conducted to a double blind, double-dummy, repeat dose design. There was a washout period between Part A and Part B of 4 to 6 weeks.

Figure 11: Study Design for Study 344



Part A Study Design

Each subject participated in one repeat dose session and was administered 320 mg orally of gemifloxacin once daily or 500 mg orally of ciprofloxacin twice daily for 10 days or until a rash was reported. Subjects were randomized to receive gemifloxacin or ciprofloxacin in a 5:1 ratio.

Subjects in whom rash was reported underwent skin biopsies, standardized photographic assessment, dermatological and clinical examinations, blood sampling for immunoglobulin levels, drug levels, liver function tests, and eosinophil counts. Individuals who reported rash stopped dosing with study medication until enrolled in Part B of the study. All subjects with gemifloxacin-associated rash in Part A were expected to take part in Part B of this protocol, with the exception of those with Type I reactions (bronchospasm, angioedema, early onset, etc.) or other severe reactions (extensive, associated with systemic symptoms, abnormal labs, mucosal involvement etc). An interim follow-up examination was conducted within 7 to 14 days of completion of dosing of Part A.

Part B Study Design

Subjects commenced Part B 4 to 6 weeks after their last dose in Part A. Depending on their Part A treatment allocation and occurrence of rash (see Figure 11), each subject entering Part B was re-randomized to receive 10 days dosing of either 320 mg orally of gemifloxacin PO, 500 mg orally of ciprofloxacin bid, or placebo. Subjects who received gemifloxacin in Part A and

reported rash were randomized to ciprofloxacin or placebo in a 3:1 ratio. Subjects who received gemifloxacin in Part A and did not report rash were randomized to gemifloxacin or placebo in a 1:1 ratio. Subjects who received ciprofloxacin in Part A and reported rash received placebo in Part B. Subjects who received ciprofloxacin in Part A and did not report rash received ciprofloxacin in Part B.

Drug administration was discontinued if rash occurred, and the same procedures as in Part A were conducted. A final follow-up examination was conducted 7 to 14 days after completion of the final dosing day in Part B.

9.4.2 Evaluation Criteria

Rash Assessment

The following assessments were made if a subject reported rash:

Clinical Rash Examination: A trained dermatologist assessed the rash using a standard Rash Questionnaire assessment within 24 hours of rash onset and prior to conducting the skin biopsy examinations. A Quality of Life assessment was conducted by subject questioning one week after the rash was reported.

Photography: Standardized photographs were taken of the rash sites.

Skin Biopsies: Three skin biopsy samples, each from unaffected and affected sites were taken. Biopsy sections underwent direct immunofluorescence examination for immunoglobulin in the skin and complement (C3) in the skin and immunophenotyping including ICAM-1, CD3 (all T lymphocytes), CD4 (T-helper lymphocytes), CD8 (T-cytotoxic lymphocytes), CD20 (all B lymphocytes) and HLA-DR (activated lymphocytes). These markers, along with any evidence of leukocytoclastic vasculitis, keratinocyte necrosis, immune complex deposition, or separation of the dermal/epidermal junction seen in conjunction with clinical signs of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), were used to judge the severity of any reaction observed. Histopathologists were blinded to subjects' drug regimen while reviewing the pathology.

Blood sampling: Blood samples for assessment of drug levels, liver function tests, eosinophils, and Epstein-Barr virus (EBV) screen were taken at time of assessment of rash.

Urine sampling: A sample was taken at the time of reporting of rash for urinalysis, including eosinophil counts.

Pharmacokinetic Parameters

Blood samples were collected for pharmacokinetic analysis in Part A only, on Days 1 and 6 (pre-dose and either at 1.5, 3, 6, and 12 h or at 1, 2, 4, 8, and 24 h following dosing).

9.4.3 Study Population

A total of 1011 healthy female subjects participated in Part A, and 873 subjects continued in Part B of the study. A total of 838 subjects completed the entire study as planned. The summary demographic statistics within and between regimens were similar.

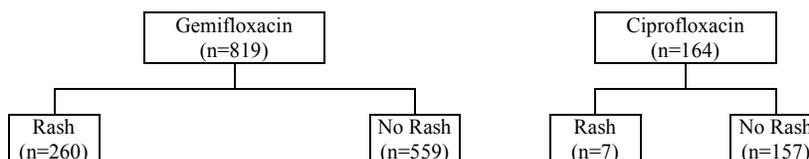
There were 138 withdrawals from Part A of this study. Of the subjects who withdrew from the study in Part A, 31 subjects withdrew due to non-rash related adverse events, and 25 withdrew due to rash related AEs. In Part B, 30 subjects withdrew; of these, 3 subjects withdrew due to rash related AEs. There were 12 non-rash related AE withdrawals. The most frequently reported AEs leading to withdrawal in the non-rash related AE group were abdominal pain, vomiting, nausea, diarrhea, and unintended pregnancy.

9.4.4 Incidence of Rash

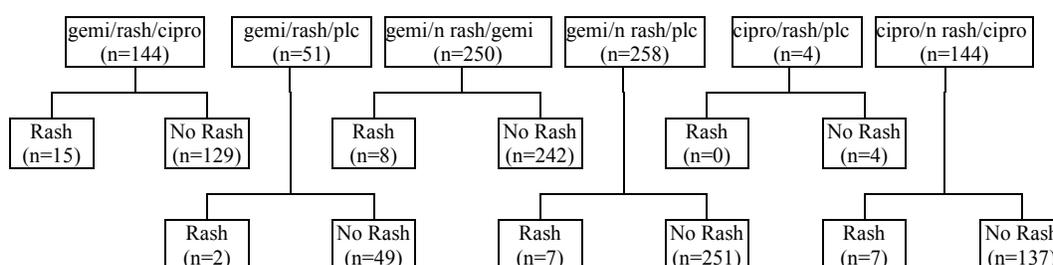
The subject disposition in the different study arms is summarized in Figure 12.

Figure 12: Subject Disposition in Part A and Part B

Part A



Part B



Part A

There were 1011 subjects entered into Part A, of which 983 were evaluable. Eight hundred and nineteen (819) subjects had received gemifloxacin (83%) and 164 (17%) received ciprofloxacin.

Two hundred and sixty (260) out of 819 (31.7%) evaluable subjects dosed with gemifloxacin and 7/164 (4.3%) evaluable subjects dosed with ciprofloxacin had a rash (this includes rash, rash erythematous and rash maculopapular) in Part A confirmed by the study dermatologist (Table 56).

Table 56: Point Estimates and 95% CI for Incidence of Rash in Part A

Regimen	Number of Subjects	Subjects with Rash	Point Estimate	95% CI	
				Normal Approximation	Exact Method
Gemifloxacin	819	260	0.317	(0.285, 0.350)	(0.286, 0.351)
Ciprofloxacin	164	7	0.043	(0.009, 0.077)	(0.017, 0.086)

This study was designed with an enriched population in order to elicit enough rashes to study and characterize. The incidence of gemifloxacin associated rash observed in part A of this study was 31.7%, similar to the predicted incidence for this enriched population, given that the study was specifically designed to elicit and describe skin reactions, which may have predisposed to

detection bias. This may explain the relatively high incidence of rash reported in all arms of this study, including the ciprofloxacin (4.3% and 4.9%) and placebo arms (ranging from 2% to 4%).

Part B

There were 873 subjects entered into Part B, of which 851 were evaluable. Of these, 195 evaluable subjects had a gemifloxacin-associated rash in Part A. 144/195 (74%) of these subjects received ciprofloxacin and 51/195 (26%) received placebo.

Cross-sensitization

Of the subjects who experienced a gemifloxacin-associated rash in Part A and who received ciprofloxacin in Part B, 15/144 (10.4%) presented with rash, as did 2/51 subjects (3.9%) receiving placebo.

There were no reports of rash amongst the 4 subjects who received placebo after having experienced a ciprofloxacin rash in Part A. Of the 144 subjects who did not have a ciprofloxacin-associated rash in Part A and were then re-challenged with ciprofloxacin in Part B, 7 (4.9%) presented with rash.

The rate of rash in subjects randomized to ciprofloxacin following gemifloxacin-associated rash in Part A (10.4%) was approximately double that for subjects rechallenged with ciprofloxacin (4.9%). However, these results must be interpreted with caution for the following reasons:

The study design included an inherent bias in the comparison of the two arms, as the Cipro/No Rash/Cipro arm excludes all subjects known to have a rash with Cipro on first exposure, whereas the Gemi/Rash/Cipro arm does not. The impact of this bias was assessed statistically using a probability model to adjust for this bias.

The observed difference (5.6%) was not statistically significant (95% CI: -1.2%, 12.4%); however, the study was not formally powered to show such a difference.

During review of the data, it became evident that the rash rate in Part B at Center 027, was higher than at the other centers. There is currently no explanation for the high rash rates observed across all regimens at Center 027. However, in light of the data observed, in particular the 100% rash rate with placebo (3/3 subjects), it was deemed appropriate to repeat the analysis, excluding this center.

Removal of the data from this center reduces the incidence of rash in all subgroups and therefore does not affect the observed trends. However, the observed difference between

the two arms (gemifloxacin/rash/cipro/rash and cipro/nrash/cipro/rash) is reduced [10.4% vs. 4.9% including Center 027 data and 5.9% versus 3.5% excluding Center 027 data].

Sub-sensitization

Of the subjects who did not experience rash on gemifloxacin in Part A and who received gemifloxacin again in Part B, eight (8/250, 3.2%) had a rash in Part B. Similarly, for the 258 subjects who received placebo in Part B, 7/258 subjects (2.7%) had a rash in Part B, suggesting no risk for sub-clinical sensitization.

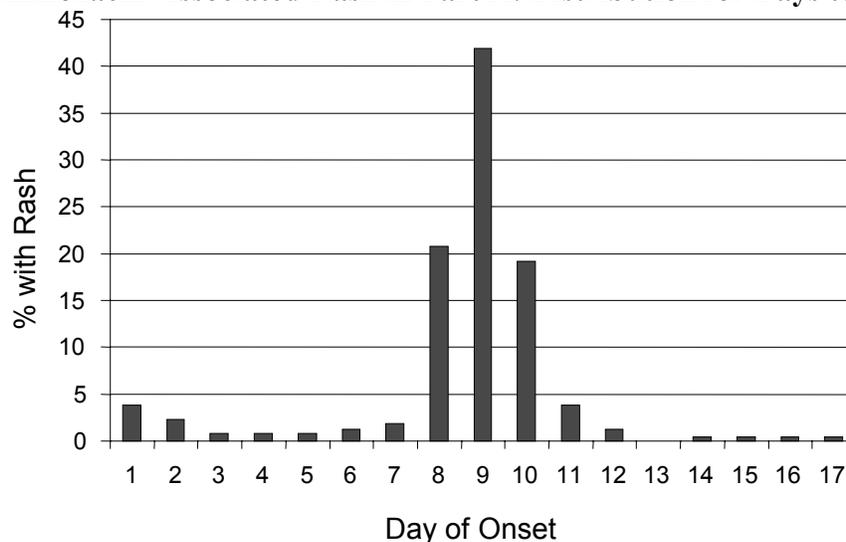
In conclusion, although this study cannot definitively establish the potential for or rate of cross-sensitization to ciprofloxacin in patients who had gemifloxacin-associated rash, the likelihood of cross-sensitization, if any, is low.

9.4.5 Description and Characteristics of Rash

Gemifloxacin Associated Rash in Part A

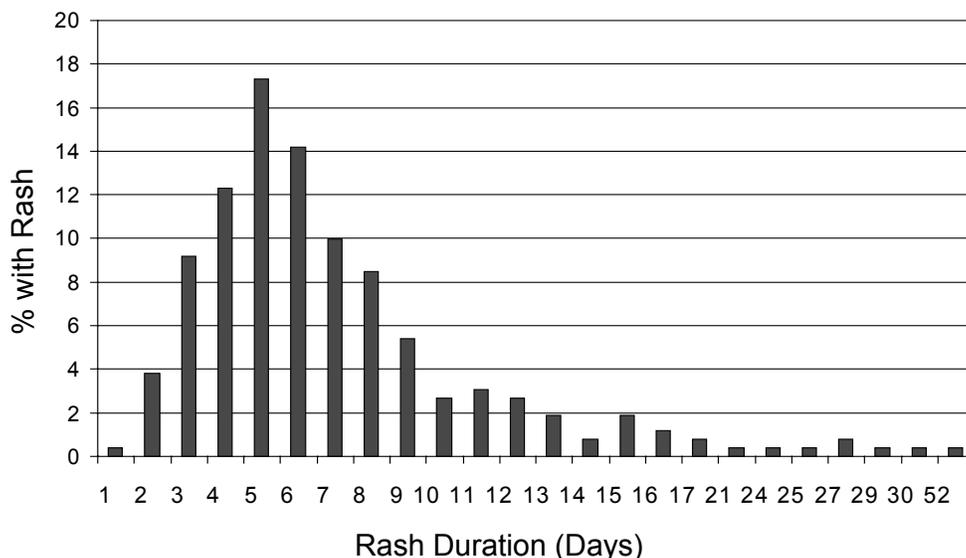
There were 260 reports of rash in the gemifloxacin arm in Part A. The majority of gemifloxacin-associated rashes occurred on days 8 to 10, with 213/260 (81.9%) subjects presenting with a rash during these three days of dosing (median day 9, range day 1 - 17) (Figure 13).

Figure 13: Gemifloxacin-Associated Rash in Part A: Distribution for Days to Onset



The median duration for gemifloxacin associated rash was 6 days (Figure 14). This is typical of the profile of rash previously observed following dosing with gemifloxacin.

Figure 14: Gemifloxacin-Associated Rash in Part A: Distributions for Duration of Rash

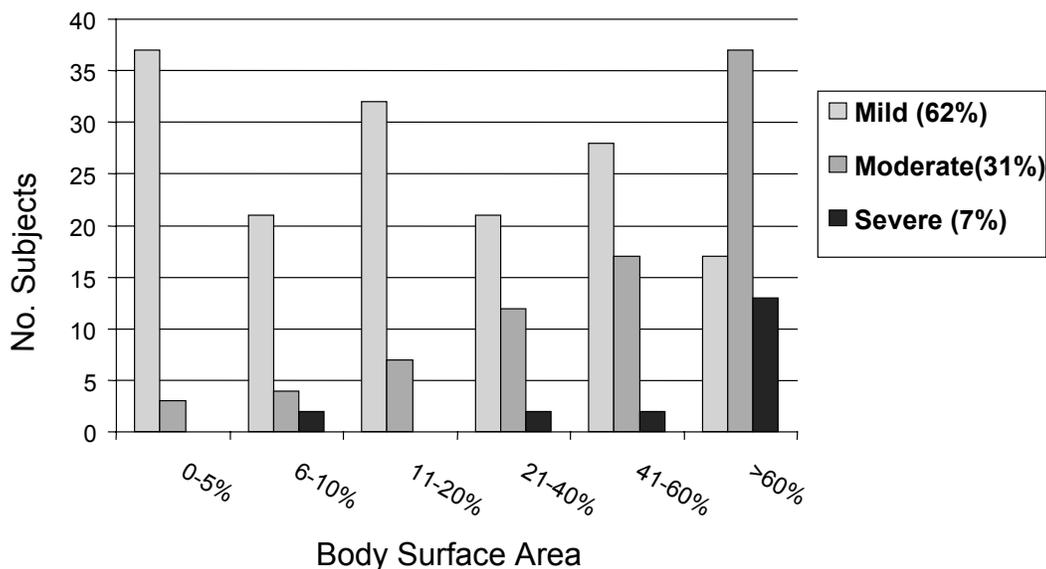


As expected, the majority (>80%) of the gemifloxacin-associated rashes were maculo-papular. In addition, many (69%) of the subjects experienced pruritus, and some of the subjects were described as having experienced urticaria (12%) plaques (11%), and skin tenderness (9%). There was no evidence of epidermal necrolysis or bullae in any of the subjects with rash.

The majority of the gemifloxacin-associated rashes were reported by the dermatologists to be mild (161/260, 62%) or moderate (80/260, 31%), and some (19/260, 7%) were considered to be severe. For the 7 subjects with ciprofloxacin-associated rash in Part A, 6 subjects reported mild rash and 1 subject reported moderate rash

The body surface area involved varied from <5% to "total body rash" (Figure 15). Investigator opinion of severity (no guidance given) seemed to correlate with the extent of the rash.

Figure 15: Gemifloxacin-Associated Rash in Part A: Severity and Body Surface Area Affected



The incidence of rash by use of hormonal therapy and previous fluoroquinolone therapy was investigated; however, there was no clear evidence to suggest that the incidence of gemifloxacin-associated rash is changed with the use of hormonal therapy or related to previous fluoroquinolone therapy.

Investigators were asked to check for pre-defined systemic signs and symptoms. Findings were as summarized in Table 57. None of these individual signs and symptoms was associated with other signs or symptoms in a way suggestive of a clinical syndrome. There were no reports of rash associated with fever and eosinophilia or of rash associated with hepatitis and eosinophilia.

Table 57: Signs and Symptoms Associated with Rash in Part A

Sign or Symptom	Number (%)* of Subjects
Urticaria	26 (10)
Facial edema	12 (4.6)
Mucosal involvement	12 (4.6)

* Calculated as percentage of the 260 subjects with gemifloxacin-associated rash in Part A.

In only 0.6% of gemifloxacin-treated volunteers (4/819) in Study 344 was urticaria actually reported as an adverse event, as opposed to being scored as urticaria on the rash assessment form. Time to onset for these 4 volunteers was 9, 23, 40, and 46 days. In one of these patients the urticaria was reported on the day of re-challenge with ciprofloxacin, 46 days after the initial gemifloxacin dose. Thus, it would appear that the number of rashes recorded as urticaria (n = 26) in Part A via the rash assessment form is artificially elevated relative to the number of volunteers for whom the adverse event was actually reported as urticaria (n = 4). The clinical course, appearance (photos), biopsy findings, and cross sensitization experience in the subjects described as having urticaria are indistinguishable from those not described as having urticaria. This suggests these are not type I hypersensitivity findings but rashes that had an urticarial appearance. The incidence of urticaria as an adverse event was similar in both the clinical Phase II/ III study database (0.5%), the overall Phase I safety data pool (0.5%), and Study 344 (0.6%).

There were few subjects with mucous membrane involvement, symptoms associated with type I reactions or systemic symptoms. Mucous membrane involvement was recorded in 12 subjects. There were concomitant findings such as dryness or aphthae. Facial edema was part of the erythema on the face by and large. One had an urticarial rash and another had diarrhea. The case report forms (CRFs) were constructed to record symptoms and signs suggestive of angioedema. In neither case were these findings suggestive of angioedema.

No association with elevated liver function test results was observed in subjects who experienced a rash in Part A. The incidence of hepatic markers was extremely low (Table 58).

Table 58: Hepatic Markers in Part A

	Rash (n=260)	No Rash n=559
ALT	0	0
Alk Phos	0	0
AST	0	2 (0.4%)
Total Bilirubin	2 (0.8%)	4 (0.7%)
GGT	0	0

GGT = γ -glutamyl transpeptidase

Increases in peripheral eosinophil counts were infrequent in any of the subjects, regardless of treatment group or presence or absence of rash (Tables 59 and 60).

Table 59: Number (%) of Subject Sessions with Eosinophil Count Transitions, No Rash

x ULN	Part A		Part B		
	Gemifloxacin 320 mg	Ciprofloxacin 500 mg	Gemi/nrash/gemi 320 mg	Gemi/nrash/plc	Cipro/nrash/cipro 500 mg
>1	22/566 (3.9)	7/156 (4.5)	2/250 (2.0)	6/252 (2.4)	5/141 (3.5)
>1.5	6/566 (1.1)	1/156 (0.6)	3/250 (1.2)	2/252 (0.8)	1/141 (0.7)
>2	4/566 (0.7)	1/156 (0.6)	1/250 (0.4)	1/252 (0.4)	1/141 (0.7)
>3	2/566 (0.4)	0	0	1/252 (0.4)	0
>5	0	0	0	1/252 (0.4)	0
>8	0	0	0	0	0

ULN = upper limit of normal (normal is 0.05 to 0.55 x 10⁹ cells/L)

Table 60: Number (%) of Subject Sessions with Eosinophil Count Transitions, Rash

x ULN	Part A		Part B				
	Gemi- floxacin 320 mg	Cipro- floxacin 500 mg	Gemi/rash/ cipro	Gemi/rash/ plc	Gemi/ nrash/gemi 320 mg	Gemi/ nrash/plc	Cipro/ nrash/cipro 500 mg
>1	12/260 (4.6)	0	0	0	0	1/7 (14.3)	0
>1.5	3/260 (1.2)	0	0	0	0	0	0

ULN = upper limit of normal (normal is 0.05 to 0.55 x 10⁹ cells/L)

Gemifloxacin and Ciprofloxacin Associated Rashes in Part B

The median day of onset of rash for all dose groups in Part B was earlier than that seen in Part A of the study for subjects dosed with gemifloxacin (Table 61).

Table 61: Summary Statistics for Day of Rash Onset in Part B

	n	Mean	SD	Median	Min	Max
gemi/rash/cipro	15	4	2.9	2	1	10
gemi/rash/plc	2	6	4.9	6	2	9
gemi/N rash/gemi	8	6	5.7	5	1	18
gemi/N rash/plc	7	6	7.9	2	1	23
cipro/rash/plc	0					
cipro/N rash/cipro	7	6	2.6	6	3	10

Data Source: Appendix C, 265805/344 study report

However, the median duration of rashes that occurred following dosing with gemifloxacin in Part B (i.e., gemi/no rash/gemi group) was similar as seen for gemifloxacin-associated rashes in Part A.

Similarly, for those subjects that received ciprofloxacin in Part B, the median rash duration was similar (i.e., 3 days in the gemi/rash/cipro group or 4 days in the cipro/no rash/cipro group) as was seen for ciprofloxacin-associated rashes in Part A. For those subjects that had a rash after receiving placebo in Part B (i.e., gemi/no rash/placebo), the median duration was 5 days, i.e., shorter than for subjects receiving gemifloxacin in Part B but longer than subjects receiving ciprofloxacin in Part B.

The appearance of the rashes seen in Part B was the same as for Part A, i.e., maculo-papular, and some subjects had pruritus.

Two subjects who experienced a rash following gemifloxacin in Part A were accidentally re-exposed to gemifloxacin in Part B. One of these subjects received a full 10-day course of gemifloxacin, while the other was withdrawn after one dose. Neither subject experienced a second rash.

Overall, rashes in Part B were milder than those described in Part A and were not associated with any systemic signs or symptoms. This further supports the view that gemifloxacin exposure does not result in a clinically significant sensitization to other members of the quinolone class.

Pruritus was reported as an AE in 11.4% (96/841) of subjects administered gemifloxacin versus 6.5% (11/170) of the ciprofloxacin group in Part A of the study. Although investigators described the rash as pruritic for many (69%) of the gemifloxacin subjects, it is of note that only 16.2% (42/260) of gemifloxacin subjects with a dermatologically confirmed rash in Part A also reported pruritus as an AE. In Part B, the frequency of reporting for pruritus as an AE was 4.3% (11/258) of gemifloxacin subjects, 7.1% (21/296) of ciprofloxacin subjects, and 4.8% (15/314) of placebo subjects. Medication was given to relieve itching in 3.2% (27/841) of gemifloxacin treated subjects compared to a single case on ciprofloxacin in Part A, 2% (6/296) on ciprofloxacin in Part B, and 1.6% (5/314) on placebo.

9.4.6 Histopathological Review of Rash

Biopsy samples were obtained from 288 subjects with rash from Parts A and B. A total of 576 slides (from unaffected and affected skin sites) were analyzed for routine histology. Immunofluorescence was done on 2880 slides (IgG, A, M & C3 plus negative and positive controls), and immunohistochemistry (immunophenotyping) was done on 4032 slides (CD3, 4, 8, 20, ICAM & HLADR plus negative and positive controls).

There were no pathological changes of clinical significance in unaffected skin. The most common finding in the affected skin was a mild superficial perivascular lymphocytic infiltrate. There were 10 cases of affected skin with moderate superficial or deep and superficial perivascular lymphocytic infiltrate. There were 10 cases with eosinophils in the infiltrate (9 affected skin samples and 1 unaffected). The lymphocytic infiltrate was T-cell type, both CD4 and CD8 cells present with no specific cell type predominance. There was activation of endothelial cells as indicated by their staining for ICAM and HLADR. This was in the absence of any evidence of vasculitis in all the biopsies. HLADR staining of dendritic cells was noted in a significant number of cases, although this was not part of the original components to be evaluated.

Immunofluorescence showed in some biopsies of affected and unaffected skin faint deposits of IgM & or C3 in dermal vessels “lumina.” One case showed linear IgM along the basement membrane in both affected and unaffected skin.

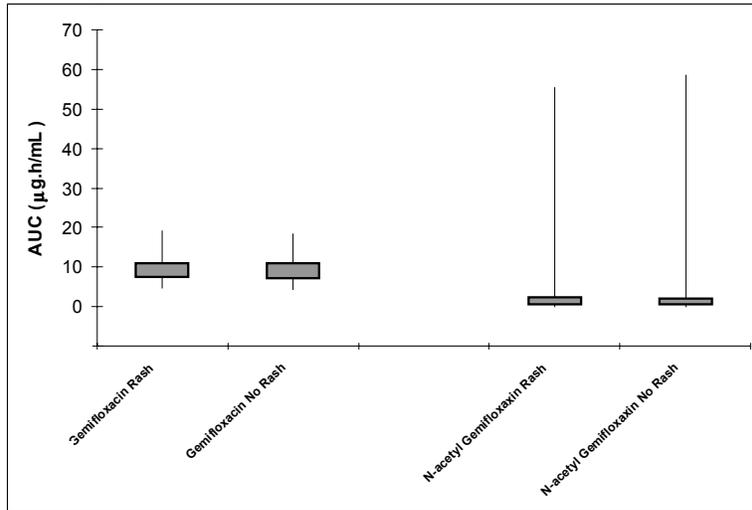
One case showed scratching excoriation, and there was one incidental case of miliaria pustulosa. It is important to note that there were no signs of epidermal necrosis, and no bulla formation in the epidermis or at the dermo-epidermal junction. There was no necrotizing vasculitis, and no pathological changes in the eccrine glands.

In summary, the histological evaluation of the biopsy samples showed a mild perivascular infiltrate of T cells without predominance of CD4 or CD8. There were no biopsy samples with signs of vasculitis, bulla formation, or epidermal or eccrine necrosis. The histopathology was consistent with the clinical observation of uncomplicated exanthematous morbilliform eruptions.

9.4.7 Pharmacokinetic Evaluation

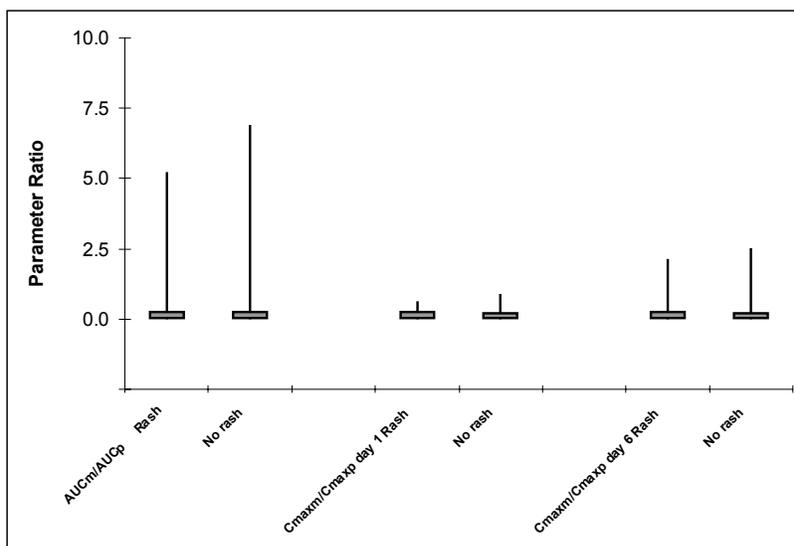
The use of sparse pharmacokinetic sampling in conjunction with population pharmacokinetic analysis of gemifloxacin and N-acetyl gemifloxacin provided accurate estimates of population pharmacokinetic parameters. Plasma concentration-time data were analyzed separately for gemifloxacin and N-acetyl gemifloxacin and included data from 838 and 837 subjects, respectively. A total of 7943 and 7934 plasma concentration-time data, respectively, were used in the final population pharmacokinetic analysis. The mean concentration-time course and 95%-confidence intervals for parent compound and metabolite concentrations were practically identical in subjects showing rash and no rash. The pharmacokinetic exposure parameters of gemifloxacin and N-acetyl gemifloxacin in subjects who experienced rash did not differ from those without rash. The summary statistics for these parameters are presented graphically as box [95% CI around geometric mean titer (GMT)] and whisker (range) plots in Figure 16.

Figure 16: AUC for Gemifloxacin and N-Acetyl Gemifloxacin in Subjects with and without Rash (Box-Whisker Plot)



As metabolic phenotype information was not formally evaluated in the pharmacokinetic model, the ratio between the AUC of the metabolite and parent compound (AUC_{met}/AUC_{par}) was used to identify potential differences between poor and fast metabolizers in terms of sensitivity to gemifloxacin. The AUC and C_{max} ratios were similar in subjects with and without rash. These results are summarized in Figure 17.

Figure 17: Pharmacokinetic Parameter Ratios in Subjects with and without Rash (Box-Whisker Plots)



The pharmacokinetic analysis showed that exposure to gemifloxacin and N-acetyl gemifloxacin in subjects who experienced rash was very similar to the exposure in subjects who had no rash, with nearly complete overlap of the 95% confidence intervals for AUC and C_{max} in these 2 sub-populations.

Despite the lack of information on the metabolic phenotype, the use of AUC_{met}/AUC_{parent} ratios provided an accurate estimate of potential differences in poor and fast metabolizers. The mean ratios and 95%-confidence intervals in subjects who experienced rash were similar to those for subjects without rash.

These findings strongly suggest that neither the differences in drug exposure nor the extent of acetylation of gemifloxacin explained the occurrence of rash.

9.4.8 Laboratory Tests

Overall there was a very low frequency of subject sessions with laboratory test results of “potential clinical concern” in all subject populations, regardless of what dose regimen they received or whether they experienced a rash or not. There were also no clinically significant changes (F3 transitions) in LFTs and eosinophils in any of the dosing regimens examined, regardless of whether they experienced a rash or not.

9.4.9 Conclusions from Study 344

Study 344, involving 1,011 young adult females, was conducted to further characterize the gemifloxacin-associated rash. The study intentionally enrolled subjects most likely to develop a rash following exposure, namely female subjects aged <40 years, who were then exposed to 10 days of treatment, which was longer than the intended duration of treatment, up to 7 days, in order to maximize the incidence of rash. The incidence of gemifloxacin-associated rash in this enriched population was 31.7%. By comparison, the overall incidence of rash in the clinical trials was 3.6%.

The results of Study 344 could not definitively establish the potential for, or rate of, cross-sensitization to ciprofloxacin in patients who had gemifloxacin-associated rash because there was an inherent bias in comparing the 2 arms; the Cipro/No Rash/Cipro arm excluded all subjects known to have a rash with ciprofloxacin on first exposure, whereas the Gemi/Rash/Cipro arm did not. However, after proper statistical adjustment and evaluation, cross-sensitization, if any, was at a low rate. There was no evidence of sub-clinical sensitization in subjects who did not develop a rash on first exposure to gemifloxacin and who were re-exposed to a subsequent course of 10 days of gemifloxacin. The characteristics of rash observed in the study were consistent with those of rash observed in the clinical trial program. There were no reports of serious cutaneous reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis and no known cases of other sequelae.

The nature of the rash was consistent with a typical, exanthematous drug eruption. The pathology seen in almost all cases was a mild, superficial, perivascular lymphocytic reaction, the classic pathology of mild drug rash. There was no evidence of pathology as seen with more severe skin reactions to drugs. The immunofluorescent findings were mild and of no clinical significance. The immunohistochemistry showed that infiltrating lymphocytes were mostly CD4+, with some CD8+ cells. There was no demonstrable predominance of CD8+ cells as is sometimes seen in serious rashes.

There was no notable difference in exposure to gemifloxacin or in extent of N-acetylation of gemifloxacin in subjects with or without rash, as indicated by AUC_{met}/AUC_{parent} ratios. The occurrence of rash as an adverse event did not therefore appear to be related to the inter-individual differences in systemic exposure to gemifloxacin, or its N-acetyl metabolite.

9.5 Cardiac Safety

9.5.1 QTc Interval Changes

Some fluoroquinolones are associated with prolongation of the electrocardiographic QT interval. Nonclinical studies, while not quantitatively predictive of clinical effect, can help to guide the level of definitive assessment of QT interval changes in the relevant species, man. Gemifloxacin caused reversible QT interval prolongation in dogs dosed intravenously, but not orally, at multiples of clinical exposure (Section 4.2). Comparative *in vitro* assays showed gemifloxacin to be of relatively low potency in prolonging APD₉₀ in Purkinje fibers or inhibiting the hERG channel. However, in accordance with recommended best practice, gemifloxacin's potential to alter the QTc interval in humans was evaluated in substantial numbers of healthy volunteers and patients. As patients were not excluded from clinical trials because of risk factors for QT prolongation, the population studied is considered to be broadly representative of that expected in clinical use of gemifloxacin.

Only subjects with paired, manual QT recordings are included in the quantitative analyses. Electrocardiogram (ECG) waveforms were recorded (≥ 3 leads simultaneously) at 25 mm/sec (10 mm/mV) for at least 3-5 complexes. QT intervals were measured manually and corrected (QTc) using the most established formula, Bazett's, by two independent cardiologists. A third cardiologist reviewed traces showing treatment-emergent abnormalities. All ECGs were analyzed in a blinded fashion. "Off-therapy" ECGs in patients were recorded either before treatment or at least 5 half-lives after the last dose of gemifloxacin; on-therapy values were obtained approximately at plasma C_{max}.

Gemifloxacin's potential to alter QTc was assessed with regard to risk factors for QTc prolongation, both general (age, gender), and individual (co-morbidities, abnormal ECG, electrolyte status, concurrent medication known to affect QTc). Co-medications capable of prolonging the QTc interval, and which compete for or inhibit cytochromes P450, particularly CYP3A4, are potentially an issue. Gemifloxacin does not inhibit and is not cleared by cytochrome P450-dependent metabolism; therefore this type of drug-drug interaction is not of concern.

Surrogate evidence of potential arrhythmias (syncope, convulsions, cardiac arrest, sudden death), and treatment-emergent changes in waveform morphology, were evaluated. Mean and individual QTc intervals were considered. Reference upper limits for the absolute QTc interval in males (450 msec) and females (470 msec), for "marked" prolongation (absolute value >500 msec), and for change from baseline in QTc interval (>60 msec) were used. Individual changes from baseline of <30 msec are generally considered unlikely to raise significant concerns about the potential risk of arrhythmias (CPMP 1997).

9.5.2 Clinical Pharmacology Studies

Evaluable manual QTc measurements were available for 1395 healthy volunteer sessions. Study 344 contributed the largest amount of repeated dose volunteer ECG data (831 subjects receiving a single dose, and 788 receiving repeated doses), and in a female population; female gender is a risk factor for QTc prolongation.

9.5.2.1 Mean QTc Change

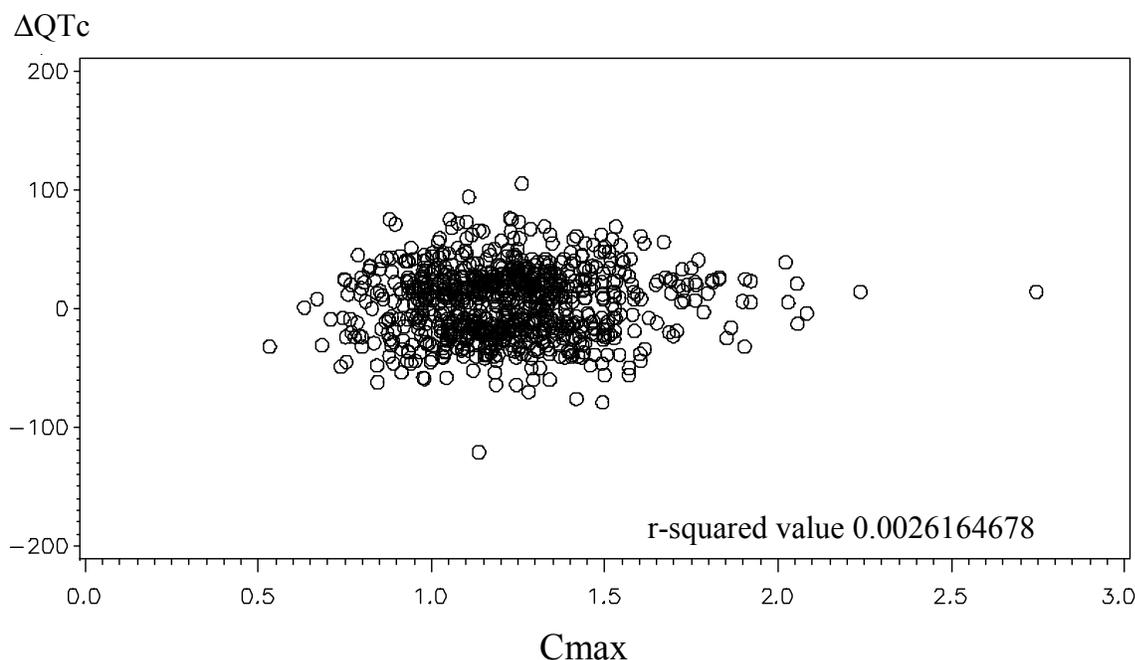
In Study 344, repeated administration of gemifloxacin or ciprofloxacin produced similar, minor increases (4.9 msec) in mean QTc compared with baseline (Table 62). Ciprofloxacin has not been associated clinically with consequences of QTc prolongation.

Table 62: Mean Change from Baseline in QTc Interval Following Repeated Dosing in Healthy Volunteers (Study 344)

	Gemifloxacin	Ciprofloxacin	
Part A	N=788	N=160	
Mean (msec)	4.9	4.9	
SD	25.10	23.85	
	Gemifloxacin	Ciprofloxacin	Placebo
Part B	N=240	N=256	N=297
Mean (msec)	8.3	12.7	5.8
SD	26.21	26.63	24.52

QTc prolongation in Study 344 subjects showed no evidence of correlation with plasma gemifloxacin C_{max} values, even when the largest observed change from baseline in QTc interval duration (i.e., on either Day 1 or Day 6) was plotted against the corresponding C_{max} value for each subject (Figure 18).

Figure 18: Highest Observed Change in QTc Interval (Δ QTc) vs. Corresponding Maximum Plasma Gemifloxacin Concentration (C_{max}) for Subjects Given a Single or Repeated Dose of Gemifloxacin in Study 344



9.5.2.2 QTc Values Outside Pre-set Reference Limits

On-therapy QTc values of potential clinical concern in non-Study 344 volunteers were distributed similarly in subjects receiving gemifloxacin or placebo. There were no clear trends for values outside the reference ranges to be more frequent with increasing dose, repeated doses, or in elderly compared with younger subjects. There was no discernible relationship between QTc and plasma gemifloxacin C_{max} values. In Study 344, few subjects had QTc values >470 msec (Table 63), and of 28 with a change in QTc >60 msec, 8 had transient increases only after the first dose. No gemifloxacin-treated subject with a QTc outside normal limits in Part A showed any abnormal values in Part B. In the overall non-patient volunteer database of 1395 gemifloxacin subject sessions with manual QT recording, absolute QTc values exceeded 450 msec in males and 470 msec in females on 16 occasions (1.1%), compared with a placebo rate of 7/415 (1.6%). Increases in QTc of >60 msec occurred on 42/1395 (3.0%) sessions in subjects given gemifloxacin, and on 17/415 (4.0%) sessions in subjects given placebo.

Table 63: Number (%) of Healthy Volunteers with QTc >470msec On-Therapy, or Change in QTc >60msec from Baseline (Study 344)

		Gemifloxacin		Ciprofloxacin			
		N=788		N=160			
Part A	Range	n	%	n	%		
QTc on-therapy	>470msec	3	0.4	2	1.3		
Change in QTc	>60msec	28	3.6	3	1.9		
		Gemifloxacin		Ciprofloxacin		Placebo	
		N=240		N=256		N=297	
Part B	Range	n	%	n	%	n	%
QTc on-therapy	>470msec	0	-	6	2.3	3	1.0
Change in QTc	>60msec	7	2.9	23	9.0	10	3.4

9.5.3 Patient Studies

Paired ECG recordings were obtained in 436 of 6775 patients (407 with paired QTc) in the gemifloxacin group and 400 of 5248 patients (380 with paired QTc) in the all-comparators group. Females and older patients were well represented in both groups (Table 64).

Table 64: Distribution of Gender and Age of Patients with Paired QTc Recordings

Demographics		Treatment Group			
		Gemifloxacin 320 mg PO		All Comparators	
		N=407		N=380	
		n	(%)	n	(%)
Gender	Male	228	(56.0)	224	(58.9)
	Female	179	(44.0)	156	(41.1)
Age (years)	≥18 to <40	64	(15.7)	57	(15.0)
	≥40 to <65	185	(45.5)	167	(43.9)
	≥65 to <75	89	(21.9)	97	(25.5)
	≥75	69	(17.0)	59	(15.5)

Approximately 45% of patients with paired QTc recordings in both groups had at least one comorbid condition predisposing to QT prolongation (Table 65). Off-therapy ECG abnormalities associated with risk factors for QT prolongation were present in 38.8% (169/436) of patients in the gemifloxacin group and 35.8% (143/400) of patients in the all-comparators group (Table 66).

Table 65: Proportion of Patients with Paired QTc Who had Co-morbid Conditions Known to Predispose to QTc Prolongation

Conditions	Treatment Group			
	Gemifloxacin 320 mg od		All Comparators	
	N=407		N=380	
	n	(%)	n	(%)
Patients with at least 1 comorbid condition known to predispose to QTc prolongation	187	(45.9)	168	(44.2)
Hypertension	130	(31.9)	103	(27.1)
Ischemic Heart Disease/Angina Pectoris	60	(14.7)	54	(14.2)
Heart Failure	31	(7.6)	21	(5.5)
Myocardial Infarction	25	(6.1)	11	(2.9)
Hypothyroidism	19	(4.7)	20	(5.3)
Atrial Flutter/Fibrillation	11	(2.7)	10	(2.6)
Alcohol Abuse/Dependence	9	(2.2)	9	(2.4)
Serum Potassium Decreased	5	(1.2)	2	(0.5)
Injury, Intracranial	4	(1.0)	0	
Mitral Valve Disorder	4	(1.0)	1	(0.3)
Tachycardia	3	(0.7)	5	(1.3)
Hypertensive Heart Disease	2	(0.5)	1	(0.3)
Extrasystoles, Ventricular	1	(0.2)	1	(0.3)

Table 66: Number (%) of Patients with Selected Off-Therapy ECG Abnormalities

ECG Abnormality*	Treatment Group			
	Gemifloxacin 320 mg PO		All Comparators	
	N=436		N=400	
	n	(%)	n	(%)
Patients ≥ 1 selected ECG abnormality	169	(38.8)	143	(35.8)
S-T Changes Nonspecific	57	(13.1)	42	(10.5)
T Wave Inversion	38	(8.7)	37	(9.3)
Right Bundle Branch Block	24	(5.5)	25	(6.3)
Q Wave >0.04 Seconds	17	(3.9)	8	(2.0)
U Wave	14	(3.2)	7	(1.8)
PVCs Nonspecific	12	(2.8)	11	(2.8)
Left Ventricular Hypertrophy	12	(2.8)	4	(1.0)
S-T Segment Depression	9	(2.1)	7	(1.8)
Left Bundle Branch Block Nonspecific	7	(1.6)	8	(2.0)
QT Interval Increased	5	(1.1)	5	(1.3)
S-T Changes Segment Elevation	4	(0.9)	7	(1.8)
Myocardial Infarction Anterior Old	5	(1.1)	2	(0.5)
T Wave Peaked	5	(1.1)	4	(1.0)
Digitalis Effect	4	(0.9)	2	(0.5)
PVCs Unifocal	6	(1.4)	5	(1.3)
Myocardial Infarction Inferior Old	4	(0.9)	6	(1.5)

Of patients with paired QTc values, 12.5% (51/407) patients in the gemifloxacin group and 16.1% (61/380) patients in the all-comparators group with paired QTc values were receiving concomitant medications associated with QT prolongation (identified from a list including antiarrhythmics, antidepressants, anti-infectives, antiprotozoals, neuroleptics, antihistamines, vasodilators, and other miscellaneous specific agents).

9.5.3.1 Mean QTc Change

Mean changes in QTc interval in all patients in the gemifloxacin and all-comparators groups for whom paired QTc measurements were available were very small and not statistically different (Table 67).

Table 67: Mean QTc Interval Change from Off-Therapy Value in Patients with Paired QTc Measurements

Change in QTc interval (msec)	Treatment Group	
	Gemifloxacin 320 mg PO	All Comparators
N	407	380
Mean	2.56	-0.39
SD	24.52	22.64
Mean Treatment Difference	2.95 msec	
95% Confidence Interval	(-0.36, 6.26)	
p value	0.08	

Further analysis of these patients by risk factors for QTc interval prolongation, including female gender (Table 68), age greater than 65 years (Table 69), presence of comorbid conditions known to predispose toward QTc interval prolongation (Table 70), and concomitant medications recognized as associated with QTc prolongation (Table 71), also showed that mean changes in QTc interval were clinically unimportant.

Table 68: Mean QTc Interval Change from Off-Therapy Value in Female Patients with Paired QTc Measurements

Change in QTc interval (msec)	Treatment Group	
	Gemifloxacin 320 mg PO	All Comparators
N	179	156
Mean	4.45	-1.36
SD	23.31	24.04
Mean Treatment Difference	5.81 msec	
95% Confidence Interval	(0.72, 10.91)	

Table 69: Mean QTc Interval Change from Off-Therapy Value in Patients with Paired QTc Measurements, and Aged over 65 Years

Change in QTc interval (msec)	Treatment Group	
	Gemifloxacin 320 mg PO	All Comparators
N	152	142
Mean	1.74	0.67
SD	26.87	23.08
Mean Treatment Difference	1.06 msec	
95% Confidence Interval	(-4.71, 6.83)	

Table 70: Mean QTc Interval Change from Off-Therapy Value in Patients with Paired QTc Measurements, and with Comorbid Conditions Known to Predispose to QTc Prolongation

Change in QTc interval (msec)	Treatment Group	
	Gemifloxacin 320 mg PO	All Comparators
N	187	168
Mean	1.52	-1.68
SD	25.58	22.19
Mean Treatment Difference	3.20 msec	
95% Confidence Interval	(-1.83, 8.22)	

Table 71: Mean QTc Interval Change from Off-Therapy Value in Patients with Paired QTc Measurements who Received Concomitant Therapy Associated with QTc Prolongation

Change in QTc interval	Treatment Group	
	Gemifloxacin 320 mg PO	All Comparators
N	51	61
Mean	-0.56	7.42
SD	29.51	18.72
Mean Treatment Difference	-7.98 msec	
95% Confidence Interval	(-17.1, 1.13)	

9.5.3.2 Distribution of On-Therapy Changes in QTc in Patients

The proportions and distribution of patients with changes in QTc from off-therapy to on-therapy were generally similar in the gemifloxacin and all-comparators groups (Table 72).

Table 72: Number (%) of Patients with Changes in QTc from Off-Therapy Value in Patients with Paired QTc

QTc Change (msec)	Treatment Group			
	Gemifloxacin 320 mg PO		All-Comparators	
	N=407		N=380	
	n	(%)	n	(%)
< -60	2	(0.5)	1	(0.3)
≥ -60 to < -50	4	(1.0)	7	(1.8)
≥ -50 to < -40	7	(1.7)	6	(1.6)
≥ -40 to < -30	24	(5.9)	20	(5.3)
≥ -30 to < 0	145	(35.6)	155	(40.8)
≥ 0 to < 30	175	(43.0)	159	(41.8)
≥ 30 to < 40	23	(5.7)	19	(5.0)
≥ 41 to < 50	17	(4.2)	11	(2.9)
≥ 51 to < 60	5	(1.2)	0	
≥ 60	5	(1.2)	2	(0.5)

Of the 5 (1.2%) gemifloxacin patients with treatment-emergent increases in QTc of >60 msec, 2 had relevant co-morbid conditions, as did 1 of 2 patients in the all-comparators group. Four of 5 gemifloxacin-treated subjects with a QTc interval change of 51-60 msec also had co-morbidities. Slightly higher proportions of patients in the gemifloxacin group had QTc values above the reference limit than in the all-comparators group, but off-therapy as well as on-therapy (Table 73).

Table 73: Number (%) of Patients with QTc Greater Than the Reference Range (>450 msec, Male or >470 msec, Female) in Patients with Paired QTc

ECG Measurement	Range	Gemifloxacin 320 mg PO		All Comparators	
		N=407		N=380	
		n	(%)	n	(%)
QTc Off-Therapy	Outside	29	(7.1)	14	(3.7)
QTc On-Therapy	Outside	34	(8.4)	21	(5.5)

Five patients (4 treatment-emergent) in the gemifloxacin group and one receiving amoxicillin-clavulanate had absolute QTc values >500 msec on-therapy (Table 74). Of those receiving gemifloxacin, one (207.057.31027) had a QTc of 512 msec off-therapy, and 503 msec on-therapy, with co-morbidity and relevant concomitant medication. Two with treatment-emergent values >500 msec had co-morbidities (011.182.25945, hypokalemia; 185.364.29739,

hypertension, left ventricular hypertrophy and PVCs, chronic obstructive pulmonary disease (COPD), pleurisy, peripheral vascular disease, coronary artery disease, anemia, glaucoma, cataracts, depression and inguinal hernia), one (011.158.05533) was receiving concomitant medication (mianserin) associated with ventricular fibrillation and ectopic beats, and one (185.357.29796) had multiple co-morbidities (left bundle branch block, coronary artery disease, COPD, left ventricular diastolic dysfunction, pulmonary edema, anemia, osteoarthritis and dementia) and relevant concurrent medication. The patient with treatment-emergent QTc >500 msec while receiving amoxicillin-clavulanate also had a co-morbid condition.

Table 74: Number (%) of Patients with QTc >500 msec in Patients with Paired QTc

ECG Measurement	Range	Gemifloxacin 320 mg PO		All-Comparators	
		N=407		N=380	
		n	(%)	n	(%)
QTc Off-Therapy	Outside	3	(0.7)	3	(0.8)
QTc On-Therapy	Outside	5	(1.2)	2	(0.5)

9.5.3.3 Treatment-Emergent Qualitative Changes in ECG Waveform Morphology

Changes in T wave and S-T segments, and treatment-emergent U waves, may indicate drug effects related to arrhythmias. Assessment of paired ECGs revealed no consistent pattern of change in patients with minor morphological alterations of ECG waveform in either the gemifloxacin or the all-comparators group (Table 75). No patient had more than one such abnormality. Two patients given gemifloxacin had treatment-emergent non-specific S-T changes or T wave inversion associated with an increase in QTc of >60 msec, but without sequelae.

Table 75: Number (%) of Patients With Paired ECGs Showing Qualitative Changes in T wave or S-T segment, and Treatment-Emergent U Wave

ECG Abnormality	Treatment Group			
	Gemifloxacin 320 mg PO		All-Comparators	
	N=436		N=400	
	n	(%)	n	(%)
U Wave	6	(1.4)	4	(1.0)
S-T Changes Nonspecific	5	(1.1)	11	(2.8)
T Wave Inversion	4*	(0.9)	5	(1.3)
T Wave Peaked	2	(0.5)	5	(1.3)
S-T Changes Segment Elevation	1	(0.2)	0	
S-T Segment Depression	1 ⁺	(0.2)	1	(0.3)
Total Patients[#]	19	(4.4)	26	(6.5)

* Treatment-emergent T wave inversion in 1 patient (049.030.11483) was later confirmed by the reviewer as normal.

+ S-T segment depression was reported in 1 patient (011.038.05278) randomized to gemifloxacin who received 1 dose of study medication (placebo) and was withdrawn prior to receiving active study medication.

Total number of patients with qualitative treatment-emergent changes in at least 1 of the tabulated ECG abnormalities

9.5.3.4 Clinical Conditions Associated with Arrhythmias

Incidences of syncope, convulsions, sudden death and cardiac arrest, which may be surrogates for drug-induced arrhythmias, are shown in Table 76.

Table 76: Number (%) of Patients with Syncope, Convulsions, Sudden Death, and Cardiac Arrest (All-Exposed Population)

Preferred Term	Gemifloxacin		All Comparators	
	N=7659		N=5549	
	n	%	n	%
Syncope	10	(0.1)	5	(0.1)
Convulsions*	1	(<0.1)	4	(0.1)
Sudden death	3	(<0.1)	0	
Cardiac arrest	7	(0.1)	5	(0.1)

* Convulsions includes the preferred terms convulsions and convulsions grand mal.

Rates of cardiac arrest reported as SAEs were low and similar in the gemifloxacin and all-comparators groups. Death occurred in 6 of 7 patients from the gemifloxacin group, and in 4 of

5 from the all-comparators group. In 5 patients (008.044.12477, 207.114.30425, 061.066.13701, 068.009.14233 and 112.012.35903) given gemifloxacin, cardiac arrest happened 1-31 days after completion of treatment. The investigator reported the event as unlikely to be related to study medication in one of these cases, and unrelated in the remainder, and to be associated with underlying disease. Four patients had serious pre-existing cardiac conditions, and in the fifth, respiratory insufficiency was associated with impregnation syndrome as a consequence of bronchogenic carcinoma. One AECB patient (070.083.04405; male, aged 70), who had decided not to visit his doctor after a study x-ray showed right lobular pneumonia, died approximately two days after starting treatment with gemifloxacin. Cardiac arrest was linked to bronchopneumopathy of the right lobe; the investigator reported that neither event was related to treatment with gemifloxacin. The seventh patient (112.070.36346; female, aged 73), with a medical history including hypertension, supraventricular tachycardia and COPD, had chest pain 3 days after starting treatment with gemifloxacin. Cardiac arrest occurred 6 days after the last dose, during cardiac catheterization scheduled as a result of the earlier chest pain. The patient was stabilized, and the event resolved. An additional patient (287.023.60078; female, aged 71), not included in Table 76 above, died 17 days after the last dose of gemifloxacin in Study 287, which was ongoing at the time of data lock. Her post-therapy ECG was normal. Cardiac ischemia and arrhythmia were evident 14 days after completion of treatment, and her subsequent death was ascribed to cardiac arrest associated with pneumonia, acute lung edema and respiratory failure. The investigator reported that none of these conditions were related to study medication.

Cardiac arrest in the 5 patients given comparator drugs was also considered to be unrelated to study medication, or unlikely to be related. Two patients (049.086.10572 and 069.129.03278) died after cardiac arrest 7 and 22 days respectively after the last dose; in one of these, polytrauma from a suicide attempt was also cited as a cause of death. Of those in whom cardiac arrest occurred during treatment, two (185.601.29472 and 012.145.10215) had pre-existing cardiac conditions, and the third (112.800.35200) had a spontaneous pneumothorax suspected to be associated with perforation of an emphysematous bulla.

The 3 sudden deaths in the gemifloxacin group were all considered by the investigators to be unrelated to study medication. In one (012.077.10306; male, aged 62) found dead one day after the last dose, an autopsy indicated pericardial tamponade due to rupture of a cardiac aneurysm related to an old myocardial infarction to be the cause of death. Another (013.047.02585; female, aged 90) died 8 days after the last dose of gemifloxacin; death was ascribed to natural causes. The patient's medical history included uterine fibroma and hysterectomy, glaucoma, arterial hypertension, anxiety, complicated cystitis and hypokalemia; the last is a potential risk factor for QTc prolongation, but there were no other pre-disposing conditions, or co-medications, of marked significance. The third (011.11.0511; male, aged 56), died on the day after the first dose of gemifloxacin. His history showed alcoholism and heavy smoking, and a fall at home prior to hospitalization for pneumonia. The study screening ECG indicated only sinus

tachycardia, and the on-therapy ECG was normal. Blood parameters included only mildly elevated AST and creatine kinase, and a slightly low hemoglobin level. The investigator reported that death was unlikely to be related to study medication.

Convulsions were more frequent in the all-comparators group than in the gemifloxacin group. In the single patient (061.063.13589; female, aged 28) given gemifloxacin, self-resolving petit mal-like symptoms occurred 3 days after the last dose, and resolved without therapy. The event was described by the investigator as of suspected relationship to treatment, but non-serious, and the patient completed the course of gemifloxacin without further incident. In the all-comparators group, generalized tonic-clonic seizure occurred on the last day of administration of cefuroxime axetil to a male aged 35 (009.572.23940), and was considered possibly related to treatment, although the consequences of previous stroke could not be excluded. Convulsions lasting 5 days after 12 days' administration of cefuroxime/clarithromycin to a male aged 82 (012.090.17923) resolved without therapy, and were probably related to treatment. An epileptic crisis 2 days after the first dose of amoxicillin/clavulanate in a male aged 85 (011.125.05668) was considered to be associated with hyperthermia resulting from failure of treatment for CAP. Two episodes of epileptic convulsions, accompanying severe asthma, 7 days after the last dose of amoxicillin/clavulanate to a female aged 51 (070.010.20421) were also considered to be unrelated to treatment.

The incidences of syncope were low and similar in the gemifloxacin and all-comparators groups. In 9 of 10 patients receiving gemifloxacin and in the 5 patients receiving comparator regimens, syncope was considered to be both non-serious and unrelated to treatment. When the event occurred during treatment, in 5 of 6 patients from the gemifloxacin group, and in the single case from the all-comparators group, dosing was continued. The patient who was withdrawn had only a brief episode of mild symptoms. Syncope was generally considered by the investigator to be either mild or moderate in intensity, but severe in 2 patients given gemifloxacin, and in one given clarithromycin. Most occurrences resolved without treatment. Two patients given gemifloxacin had ongoing syncope at the time of the last study visit. Syncope (collapse) in the remaining patient (061.011.13158; male, aged 67) from the gemifloxacin group was considered to be a SAE. This patient, who had a history of pulmonary fibrosis, ischemic heart disease, right bundle branch block, emphysema, anasarca, cardiomyopathy, cardio-respiratory insufficiency, and auricular fibrillation, collapsed following the fifth dose, and treatment was discontinued. He was diagnosed with left heart failure and respiratory failure, and after initial improvement, died of subtotal pulmonary embolism 6 days after medication was stopped. An autopsy showed chronic heart failure associated with bullous emphysema and chronic bronchitis. Both the initial collapse and death were considered to be unrelated to treatment with gemifloxacin, and to be associated with the patient's underlying condition.

No incidents of torsades de pointes were reported in patients from either group who exhibited cardiac arrest, sudden death, syncope, or convulsions. Concomitant medications potentially

linked with QTc interval prolongation showed no evident relationship to incidence or severity of these adverse events.

9.5.4 Patients Receiving Intravenous Gemifloxacin in Phase III Studies

QTc data from paired ECGs are available from patients who received gemifloxacin during development of a clinical intravenous formulation. The program was discontinued because of lack of bioequivalence between the 320 mg oral dose and the 250 mg intravenous dose of gemifloxacin. As a result, the three Phase III intravenous formulation studies (106, 107, and 111) did not complete their targeted accrual, but the aggregated data provide paired ECG comparisons for 105 gemifloxacin- and 115 comparator-treated subjects. The additional data are substantive, as they enhance the pool of subjects who represent the general population of older patients with CAP who may also have cardiac co-morbidities and be receiving drugs that increase the risk of QT prolongation. Additionally, the mean C_{max} associated with intravenous administration of 250 mg gemifloxacin was approximately 33% higher than that achieved with the 320 mg oral dose (1.6 $\mu\text{g}/\text{mL}$ vs. 1.2 $\mu\text{g}/\text{mL}$), and attained slightly more rapidly (T_{max} c. 1 h).

9.5.4.1 Effects on QTc

Intravenous gemifloxacin had a mild effect on the QTc interval; the mean change from baseline at 50-60 minutes after administration was 1.9 msec (SD 21.55), and in the 35 subjects with off-therapy and 2-3 days on therapy values, the mean change was -2.83msec (SD 24.13).

The proportions and distribution of patients with changes in QTc from off-therapy to on-therapy were generally similar in the gemifloxacin and all-comparators groups. None of the gemifloxacin subjects assessed either 50-60 minutes post dosing (Table 77) or 2-3 days post dosing had QTc values outside the reference limits.

Table 77: Change in QTc From Off-Therapy Baseline to On-Therapy (50-60 Minutes) For Patients With a Paired QTc Recording: Intravenous Population

Change in QTc (msec)	Treatment Group			
	Gemifloxacin 250 mg od		All-Comparators	
	N=105		N=115	
	n	(%)	n	(%)
< -60	1	(1.0)	0	
≥ -60 to < -50	1	(1.0)	4	(3.5)
≥ -50 to < -40	1	(1.7)	3	(2.6)
≥ -40 to < -30	6	(5.7)	6	(5.2)
≥ -30 to < 0	34	(32.4)	38	(33)
≥ 0 to < 30	54	(51.4)	53	(46.1)
≥ 30 to < 40	5	(4.8)	3	(2.6)
≥ 41 to < 50	3	(2.9)	5	(4.3)
≥ 51 to < 60	0		0	
≥ 60	0		3	(2.6)

Of the 35 subjects with paired off-therapy and 2-3 days on-therapy ECGs that were assessed, all except one subject had QT interval increases <30 msec. The other subject had a QT interval change in the range 40-49 msec.

9.5.4.2 QTc Prolongation for Other Quinolones

For comparison, mean prolongation QTc times for other quinolones are shown in Table 78.

Table 78: QTc Interval Prolongation of Quinolone Antibiotics

	Sparfloxacin	Grepafloxacin	Moxifloxacin	Levofloxacin	Trovafloxacin	Gatifloxacin	Gemifloxacin
QTc interval prolongation in humans	Yes	Yes	PO minimal	Minimal	No	Minimal	Minimal
Mean ± SD QTc interval prolongation in humans	PO 10.3 ± 27.6 msec	PO 8 msec	PO 6 ± 26 msec, IV 12.1 msec	4.6 ± 23 msec	No data	PO and IV 2.9 ± 16.5 msec	PO 2.6 ± 24.6 msec
Number of subjects	1489		787			55	407

Ball et al. 1999; Samaha 1999; Iannini et al. 2000; Levaquin (levofloxacin) package insert

9.5.5 Conclusion

Oral dosing of gemifloxacin, 320 mg PO, was associated with only a small, clinically insignificant, mean increase in QTc interval in a substantial population of patients assessed using paired, manual ECG measurements. The distribution of changes in QTc was also consistent with that in non-patient volunteers, and with the distribution of changes produced by comparators. The few patients with treatment-emergent QTc values greater than 500 msec had significant comorbidities and/or concomitant medications known to cause QT prolongation. Neither these predisposing factors, age, gender (both risk factors for QTc prolongation), nor higher systemic concentrations of gemifloxacin associated with intravenous administration, had any significant influence on the overall distribution of QTc changes.

There was no evidence of effect of pre-existing minor waveform abnormalities on QTc, and no treatment-emergent pattern of such abnormalities. Patterns of clinical conditions potentially associated with arrhythmia generally did not differ between the gemifloxacin and all-comparators groups, and both sudden deaths and cardiac arrests after gemifloxacin administration were considered by investigators not to be related to study medication. There were no cases of torsades de pointes in any group.

Overall, in-depth evaluation of mean and individual measurements, with regard to known risk factors, supports the conclusion that oral gemifloxacin is very unlikely to cause clinically significant QTc prolongation in a wider patient population.

9.6 Hepatic Safety

Hepatotoxicity was observed in pre-clinical studies conducted in dogs. The hepatotoxicity seen in dogs likely depended on deposition of crystals of gemifloxacin in the biliary tract, followed by local impedance of bile flow and resulting damage by bile salts to principally periportal hepatocytes ('cholate stasis'). Humans are predicted to be protected, both by a lesser burden on biliary secretion and by biliary pH favoring maintenance of gemifloxacin in solution, however the occasional rise in liver function tests may be explained by the mechanism of reversible "injury" seen in dogs. This may have been more evident in the human pharmacology studies where subjects were treated with 640 mg daily of gemifloxacin and 2.1% were noted to demonstrate elevation of liver transaminases, more than twice the upper limit of normal, quite often in association with demonstrable rises in alkaline phosphatase. In no cases did any of these subjects exposed to this higher dose of gemifloxacin (or any of the 6775 patients exposed to the 320 mg dose of gemifloxacin) exhibit laboratory findings consistent with Hy's Law (elevation of bilirubin above 3 mg/dL in conjunction with significant elevation of liver transaminases), which has been identified as a potential sentinel for the risk of severe and irreversible drug-induced hepatocellular injury.

Table 79 presents the numbers and percentages of patients in each treatment group who had liver function test results of clinical concern at the on-therapy and end-of-therapy visits. These values were flagged F2F3, denoting values that changed (increased or decreased) from baseline by more than a specified amount and also fell outside an extended normal range.

The incidence of liver function tests of clinical concern was low in both treatment groups at both visits (Table 79).

Table 79: Number (%) of Patients with Liver Clinical Chemistry Values Outside the F2F3 Range at the On-Therapy and End-of-Therapy Visits

Visit/Liver Clinical Chemistry Variable	F2F3 Range	Treatment Group			
		Gemifloxacin		All	
		320 mg PO		Comparators	
		N = 6775		N = 5248	
		n/N*	(%)	n/N*	(%)
On-Therapy Visit					
ALT	High	63/4307	(1.5)	35/3840	(0.9)
AST	High	48/4307	(1.1)	30/3840	(0.8)
ALK-Phos	High	15/4352	(0.3)	12/3876	(0.3)
Total Protein	Low	4/4322	(0.1)	3/3855	(0.1)
Albumin	Low	14/4361	(0.3)	3/3887	(0.1)
Total Bilirubin	High	15/4348	(0.3)	2/3871	(0.1)
LDH	High	0/187		1/185	(0.5)
End-of-Therapy Visit					
ALT	High	41/5331	(0.8)	37/3940	(0.9)
AST	High	22/5330	(0.4)	10/3937	(0.3)
ALK-Phos	High	8/5371	(0.1)	4/3980	(0.1)
Total Protein	Low	2/5364	(<0.1)	0/3961	
Albumin	Low	7/5395	(0.1)	0/3993	
Total Bilirubin	High	11/5364	(0.2)	5/3972	(0.1)

Note: ALT (SGPT) = alanine aminotransferase; AST (SGOT) = aspartate aminotransferase; Alk-Phos = alkaline phosphatase.; LDH = lactate dehydrogenase

*n/N = number of patients with flag/number of patients evaluated for the particular parameter.

Gemifloxacin treatment was not associated with any consistent liver clinical chemistry finding. Treatment-emergent changes of potential clinical concern in liver values were very infrequent. No marked or consistent differences between the gemifloxacin 320 mg PO and the all-comparator groups were seen in F2F3-flagged values (Table 80).

Table 80: Number (%) of Patients with Treatment-Emergent Liver Function Tests within the Specified Ranges at the On-Therapy and End-of-Therapy Visits

Visit/ Laboratory test	Range	Gemifloxacin 320 mg PO N=6681*		All Comparators N=5174*	
		n	(%)	n	(%)
On-Therapy Visit					
Alanine Aminotransferase	<ULN	3800	(95.3)	3443	(96.0)
	ULN to <2xULN	162	(4.1)	127	(3.5)
	2 to <4xULN	26	(0.7)	15	(0.4)
	4 to <6xULN	1	(<0.1)	2	(<0.1)
	≥8xULN	0		1	(<0.1)
Alkaline Phosphatase	<ULN	4007	(98.3)	3607	(98.2)
	ULN to <2xULN	61	(1.5)	62	(1.7)
	2 to <4xULN	6	(0.1)	3	(0.1)
	4 to <6xULN	1	(<0.1)	0	
Aspartate Aminotransferase	<ULN	3824	(95.8)	3512	(96.7)
	ULN to <2xULN	141	(3.5)	106	(2.9)
	2 to <4xULN	23	(0.6)	14	(0.4)
	4 to <6xULN	1	(<0.1)	1	(<0.1)
	6 to <8xULN	1	(<0.1)	0	
Total Bilirubin	<ULN	4046	(99.0)	3621	(99.1)
	ULN to <2xULN	38	(0.9)	34	(0.9)
	2 to <4xULN	3	(0.1)	0	
End-of-Therapy Visit					
Alanine Aminotransferase	<ULN	4752	(95.7)	3545	(95.6)
	ULN to <2xULN	191	(3.8)	135	(3.6)
	2 to <4xULN	22	(0.4)	27	(0.7)
	4 to <6xULN	2	(<0.1)	2	(<0.1)
Alkaline Phosphatase	<ULN	5006	(98.6)	3712	(98.3)
	ULN to <2xULN	69	(1.4)	64	(1.7)
	2 to <4xULN	4	(0.1)	2	(0.1)
Aspartate Aminotransferase	<ULN	4892	(97.8)	3673	(97.9)
	ULN to <2xULN	99	(2.0)	72	(1.9)
	2 to <4xULN	13	(0.3)	6	(0.2)
Total Bilirubin	ULN	5009	(98.6)	3703	(98.7)
	ULN to <2xULN	69	(1.4)	50	(1.3)
	2 to <4xULN	3	(0.1)	0	

* Total includes all patients who had values within the normal range at screening but at least one abnormal value at either the on-therapy or end-of-therapy visit.

An earlier quinolone, temafloxacin, demonstrated a cluster of clinical effects, including hepatotoxicity, the so called “temafloxacin syndrome”. Patients are defined as having temafloxacin syndrome if a single blood specimen meets all of the following criteria:

Bilirubin increase from baseline greater than or equal to 1.0 mg/dL or greater than or equal to 17 μ mol/L

Serum creatinine increase from baseline greater than or equal to 0.8 mg/dL or greater than or equal to 73 μ mol/L

Hemoglobin decrease from baseline greater than or equal to 2 g/dL or greater than or equal to 1.24 mmol /L.

None of the gemifloxacin treated subjects met these criteria.

9.6.1 Independent Review of Liver Findings

The liver findings of gemifloxacin were reviewed by Dr. Paul Watkins, Professor of Pharmacotherapy, University of North Carolina, Chapel Hill, NC. Dr. Watkins reviewed all cases in the gemifloxacin safety database using conservative criteria, ALT \geq 2 x ULN or total bilirubin \geq 1.5 mg/dL. His analysis of liver functions after dosing with Factive are summarized as follows:

The most sensitive and specific test available to detect hepatocellular injury is serum ALT; serum bilirubin elevations associated with hepatocellular injury occur only when that injury is severe. There were no patients in the gemifloxacin clinical trials database who experienced bilirubin elevations to > 1.5 mg/dl as a result of treatment-emergent hepatocellular injury. At the 320 mg dose, there were no treatment-associated ALT elevations exceeding 8 times the ULN among those patients with normal ALT at screening. Among patients with abnormal ALT at screening, there was only one patient who experienced an ALT elevation exceeding 8 x ULN and where gemifloxacin may have contributed to the injury observed. In this case, the incremental injury possibly attributable to gemifloxacin resulted in a 5-fold elevation in ALT relative to the screening value, which itself was approximately 2.5 x ULN. Among patients who received 640 mg doses of gemifloxacin, the incidence of ALT elevations >2 X ULN was higher with gemifloxacin treatment (13/615, 2.1%) relative to treatment with the comparator, ciprofloxacin (2/627, 0.3%). Two of the patients receiving 640 mg experienced asymptomatic ALT elevations >8 x ULN, which were rapidly reversible.

The precise mechanism for the ALT elevations observed in a minority of patients receiving 640 mg gemifloxacin is unclear. However, there is no evidence of an immunologic basis or of other

mechanisms that have been previously associated with acute liver failure or irreversible liver injury. The available data are compatible with “cholate stasis” which appears to account for the toxicity observed in the dog.

The available data are most consistent with first pass liver exposure (and not systemic exposure) as being the most relevant determinant of toxic response. For a drug that is well absorbed like gemifloxacin, first pass liver exposure should be chiefly a function of oral dose, with relatively little interpatient variability. Hence, the differences in incidence of ALT elevations observed between ciprofloxacin and double dose (640 mg) gemifloxacin do not raise significant safety concerns for the 320 mg dose.

Dr. Watkins concluded that the data, in aggregate, do not suggest a significant hepatotoxicity risk with gemifloxacin, in particular at the proposed dose of 320 mg, and as noted above, the increased incidence and height of ALT elevations at the 640 mg dose do not raise significant safety concerns about the 320 mg dose.

9.7 Safety Conclusions

Overall, gemifloxacin 320 mg PO was well tolerated in the clinical studies.

The incidence of rash in the Combined population was higher for the gemifloxacin group (all durations) than for the all-comparators group, 3.6% vs. 1.1%, respectively. Most cases of rash were of mild or moderate intensity. The rash is self-limiting and not associated with any of the features of a more severe cutaneous drug reaction, which carries a risk of significant morbidity or mortality. The cross sensitization potential to other quinolones is low, and there is no subclinical sensitization potential. There were no instances of Stevens-Johnson syndrome or toxic epidermal necrolysis and no other known sequelae to any of the reported rashes.

Use of gemifloxacin was associated with small prolongations in the electrocardiographic QTc interval. These prolongations were not clinically meaningful.

Gemifloxacin treatment was not associated with any consistent liver clinical chemistry finding. Treatment-emergent changes of potential clinical concern in liver values were very infrequent. No marked or consistent differences between the gemifloxacin 320 mg PO and the all-comparator groups were seen in F2F3-flagged values.

10. DISCUSSION

Multidrug resistance in many pathogenic bacteria is a widely reported phenomenon of increasing concern both to the individual patient and to society as a whole (Butler et al. 1996; Cunha and Shea 1998; Doern et al. 1998). Increasing usage of each antibiotic class has been accompanied by an increase in bacterial resistance to that class of antibiotic over time.

Usage of the newer quinolones - levofloxacin, moxifloxacin and gatifloxacin - and off-label use of ciprofloxacin for the treatment of respiratory infections has increased with a concomitant increase in the rate of quinolone-resistant strains of *S. pneumoniae* in the U.S., Canada, and Europe (Chen et al. 1999; Jones et al. 2000; Empey et al. 2001; Zheng et al. 2001; Anderson et al. 2002; Davidson et al. 2002; Ferraro 2002; Ross et al. 2002). Indeed, recently the results were presented of a nationwide surveillance program that showed pockets of high prevalence of resistance in some regions of the U.S. with rates as high as 22% (Ferraro 2002).

This scenario is exactly how pneumococcal resistance to penicillin emerged in the 1980s. The overall penicillin-resistance prevalence rates were only 2% in the early 80s. But even then, there were regions in the country where resistance was between 15-20%, foreshadowing the high cross-the-board rates we have today.

With the continuing increase in the prevalence of community-acquired respiratory pathogens with resistance to a variety of antimicrobial agents, more potent agents with improved activity, particularly versus *S. pneumoniae*, are clearly needed. Gemifloxacin, by virtue of its inherent *in vitro* potency, pharmacokinetics, and proven clinical efficacy against both antibiotic sensitive and resistant strains of bacteria responsible common respiratory diseases, represents an important new therapeutic option for treatment of CAP and AECB.

Gemifloxacin has a favorable benefit/risk and represents the “best in class” quinolone for the treatment of respiratory infections, particularly in an older patient population, in an era of increasing antibiotic resistance.

Mechanisms of quinolone resistance in *S. pneumoniae* include mutations in the *parC* or *gyrA* gene (step one mutation) or both genes (step two or double mutation). Quinolone resistance is a class phenomenon and quinolone-resistant *S. pneumoniae* exhibit increased MICs to all quinolones. In the case of a single mutation, most *S. pneumoniae* isolates become resistant to the currently marketed quinolones. Gemifloxacin by virtue of its low MIC to *S. pneumoniae* remains below its predicted breakpoint. Only the *gyrA/parC* double mutant caused a significant increase in gemifloxacin MIC. Gemifloxacin is the only quinolone to retain significant anti-pneumococcal activity in the face of quinolone resistance. In light of these facts it is probable

that gemifloxacin will increase in importance as part of the armamentarium of physicians in treating respiratory infections as the incidence of bacterial drug resistance increases.

Gemifloxacin was found to have the lowest MICs of all the marketed quinolones to both penicillin- and macrolide-resistant *S. pneumoniae*. AUC_{24}/MIC and C_{max}/MIC parameters for gemifloxacin predict that gemifloxacin will have the highest efficacy and lowest resistance generation compared to the currently marketed quinolones for these drug-resistant bacteria. Gemifloxacin also has excellent activity against the other major respiratory pathogens, *H. influenzae*, *M. catarrhalis* and the atypical organisms, *Legionella pneumophila*, *Chlamydia trachomatis*, and *Mycoplasma pneumoniae* with activity against these pathogens being comparable to the activity seen with other marketed quinolones. Thus based upon *in vitro* data, gemifloxacin can be expected to be efficacious against the usual respiratory tract pathogens.

In clinical trials gemifloxacin's anti-bacterial activity and pharmacokinetic parameters have translated into convincing efficacy versus multiple comparator drugs in AECB and CAP. Included in the demonstrated clinical efficacy was a reduction in the duration of hospitalization and the rate of relapse in AECB patients.

Chronic bronchitis is a recurring disease process and thus the demonstration of efficacy as measured by reduced duration of hospitalization and relapse rates has obvious potential benefits to individual patients and to the health care system. Among these potential benefits – in addition to those already stated – would be an improved quality of life, due to the decreased time spent in the hospital and seeking treatment for relapsed. In addition, society would benefit from being able to utilize health care resources on other patients.

With respect to CAP, gemifloxacin has been shown to be effective not only for the treatment of CAP as a whole, but also for the treatment of all degrees of severities of CAP. Such efficacy will enable physicians safely and appropriately to utilize gemifloxacin as their primary therapy, without regard to the underlying severity of their disease.

Gemifloxacin can be expected to be particularly advantageous for the elderly population with CAP for two reasons: its oral formulation and its safety profile. Gemifloxacin is currently only available as an oral medication, but possesses an excellent oral bioavailability (~71%). The sponsor concludes that in light of the clinical efficacy trial results and the bioavailability data, oral gemifloxacin can be effectively used for the treatment of all severities of CAP. This will enable patients to avoid the need for vascular access for parenteral therapy and will thus allow for better ambulation of patients. Such ambulation can be expected to be advantageous in preventing complications such as deep venous thrombosis, and in improving ventilation. Such attributes are particularly important in an elderly population with CAP.

With respect to its safety attributes among elderly patients it should be noted that there are an increasing number of effective medications for the treatment of a variety of diseases more prevalent in older age groups. Multiple drugs are frequently prescribed for underlying cardiovascular and chronic respiratory conditions. Renal and hepatic impairment may also occur in this population. Physicians thus face difficult choices in selecting drugs without potential for drug or concomitant disease interactions in this group. The lack of CYP450-mediated drug interaction or dosage modification requirement in hepatic and mild-moderate renal impairment, strongly favor the benefit/risk for the use of gemifloxacin, particularly in this population.

Gemifloxacin has been documented to have a favorable safety profile among the population as a whole. Among the 6775 patients who have received gemifloxacin at 320 mg in clinical trials, the overall adverse event profile was equivalent to that seen in the control groups.

As evidenced by the lack of any cases of severe ALT elevation or significant total bilirubin elevation, the hepatic problems occasionally reported with other fluoroquinolones do not appear to be a problem with gemifloxacin. Similarly, the lack of a significant increase in QTc duration indicates that gemifloxacin does not possess cardiac arrhythmia generating potential.

The only adverse event consistently reported to occur more frequently with gemifloxacin than with control therapy was rash, occurring in 3.6% of patients overall treated with gemifloxacin vs. 1.1% for the all-comparators group. Importantly, in approximately 87% of cases, the rash was either mild or moderate in severity. The clinical, histopathological and immunofluorescence findings are those of a mild exanthematous drug eruption. None of the hallmarks presaging more severe skin reactions (lichenoid or dense lesions, significant IgM levels in lesions or CD8-predominant lymphocyte infiltrates) was observed. None of the subjects developed more serious dermatologic reactions known to be associated with significant morbidity or mortality such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or evidence of anaphylaxis. Therefore, although the rash was not an uncommon event, it was rarely clinically severe. More importantly, in no cases was it serious, using either clinical or regulatory criteria. The sponsor believes that given the unique attributes of gemifloxacin and its demonstrated clinical activity in treatment of these diseases, even in cases involving bacterial organisms resistant to other antibiotics, the risk/benefit ratio for gemifloxacin strongly favors treatment with this agent in these conditions.

11. RISK MANAGEMENT PLAN

11.1 Introduction

In the post-marketing period, GeneSoft Pharmaceuticals (LG Life Sciences U.S. commercialization partner) will continue working to optimize gemifloxacin's safety through a number of techniques. These will include monitoring of spontaneous adverse event reports, minimizing the risks of off label use through the use of blister packs and physician education, and the implementation of a phase 4 safety study. Prior to the resubmission of the NDA, GeneSoft Pharmaceuticals made the determination that the best indications would be those to treat lower respiratory tract infections. The patient population is predominantly over 40 years age, approximately equally divided between males and females, and the clinical efficacy data from the AECSB and CAP studies support short duration of treatment. Additional indications have been previously requested, including urinary tract infection (UTI) and acute bacterial sinusitis (ABS) (7days treatment), and while gemifloxacin demonstrated effectiveness, GeneSoft Pharmaceuticals is not requesting marketing approval for these indications at this time.

11.2 Spontaneous Reports

The spontaneous adverse event monitoring will be conducted using routine solicitation and compilation of adverse event reports. Solicitation will be emphasized during meetings between Genesoft Pharmaceutical marketing representatives and prescribing physicians. As per regulations, unexpected SAEs will be reported to the FDA within 15 days of initial receipt of the report, and requests for additional information will be sent to the reporters. All adverse events will be reported as part of the quarterly reports to the FDA. In addition, requests for additional information will be sent to all reporters of dermatological adverse events: whether serious or non-serious.

11.3 Off Label Use Minimization

The proposed label for gemifloxacin is to state that the indication is for a maximum of 7 days of therapy. In order to minimize the risk of off label use – use for more than 7 days – gemifloxacin will be dispensed in fixed dose packs containing either 5 or 7 tablets: 5 for use in patients with AECSB, and 7 for patients with CAP. The company has withdrawn bottle presentation of the drug from the NDA and limited the use of 30-day dispensing packs to hospital pharmacies. It is anticipated that the use of the fixed dose pack will increase gemifloxacin's use according to its label, and thereby decrease the risks of toxicity.

The company has conducted a retrospective drug utilization study that demonstrates that fixed dose packs of drugs led to <1% prescribing of extended courses of treatment compared to 15 to 28% with bottles of tablets or capsules (study report is included in Appendix 1).

Marketing representatives will emphasize the importance of prescribing gemifloxacin according to the label during all meetings with prescribing physicians, thus further decreasing the risk of patients receiving gemifloxacin for more than the labeled duration.

11.4 Phase 4 Study

Genesoft Pharmaceuticals will also conduct a phase 4 safety study. This study's objectives are to better define the incidence and outcome of rash in patients with CAP and AECCB who are treated with gemifloxacin. This study is to be a large simple study design. It is anticipated that this study will better characterize the rash and will provide further support and statistical power to the conclusion that the rash associated with gemifloxacin does not result in significant morbidity.

Through the use of these various methods, GeneSoft Pharmaceuticals intends to minimize the risks of toxicity from the use of gemifloxacin. These methods will also allow for early identification of any safety issues that need to be addressed and thereby allow them to be resolved in a timely manner.

12. CONCLUSION

In conclusion, gemifloxacin, by virtue of its inherent *in vitro* potency, pharmacokinetics, and proven clinical efficacy against both antibiotic sensitive and resistant strains of bacteria responsible common respiratory diseases, offers unique benefits, while possessing a risk profile equivalent to that of currently marketed antibiotics, including other fluoroquinolones. Gemifloxacin represents an important new therapeutic option for treatment of CAP and AECB, particularly those cases involving resistant organisms.

On the basis of these observations, the sponsor believes gemifloxacin has a benefit/risk profile justifying marketing approval.

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CDC 2002

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**APPENDIX 1: RETROSPECTIVE DRUG UTILIZATION STUDY TO ASSESS THE
LIKELY PREVALENCE OF GEMIFLOXACIN ASSOCIATED RASH IN FEMALES
LESS THAN 40 YEARS OF AGE RECEIVING GEMIFLOXACIN FOR GREATER
THAN 7 DAYS UTILIZING FIXED DOSAGE PACKAGING**

**Retrospective Drug Utilization Study to Assess the Likely Prevalence of
Gemifloxacin Associated Rash in Females Less Than 40 Years of Age
Receiving Gemifloxacin for Greater Than 7 Days Utilizing Fixed Dosage
Packaging**

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Introduction

Gemifloxacin is a fluoroquinolone antibiotic developed for the treatment of respiratory tract infections, community acquired pneumonia (CAP) and acute exacerbations of chronic bronchitis (AECB). Gemifloxacin usage is associated with an increased rate of exanthematous drug rash. Multivariate analysis of the clinical trial database demonstrates that factors associated with increased rate of rash include longer duration of therapy, female gender and age less than 40 years. These factors appear to be additive. The rash rate associated with gemifloxacin usage in females, less than 40 years old dosed with gemifloxacin for 10 days has been assessed in a phase I study, 344. This study was specifically designed to trigger rash so that it could be fully characterized. The rash rate in this study population was 31.7% [35.1% = upper limit of the 95% confidence interval]. It is important to understand the likely impact of gemifloxacin usage on this subgroup of patients in community use of the drug in the event the drug is approved for use for the treatment of CAP and AECB.

The sponsor is proposing risk management initiatives to minimize the likelihood of patients being prescribed courses of gemifloxacin therapy likely to lead to increased rates of rash. These include seeking approval for gemifloxacin therapy for a maximum of 7 days duration of therapy and making the product available in the community only as 5 and 7 day fixed dose packs. Gemifloxacin will not be available as free tablets in bottles.

It is well recognized that physicians do not necessarily restrict their prescribing habits to the labeled treatment duration of drugs, so it is important to explore off label prescribing patterns of fixed dosage packs of antibiotics and the effect of repeat prescriptions within a short time of the initial treatment course (less than 28 days) that may effectively constitute “back to back” prescribing of gemifloxacin. This needs to be explored within the context of the overall target population for CAP and AECB and in the real world situation in the community rather than in a controlled trial setting. This analysis is needed to properly assess the risk/benefit for gemifloxacin in the relatively uncontrolled setting of a marketed drug and to assess the likely effectiveness of the risk management strategies proposed by the sponsor for this particular subgroup of patients.

It is possible to model the likely community based prescribing patterns of gemifloxacin using antibiotic utilization data collected from physicians and pharmacies by marketing organizations. The data were collected from large cohorts of community physicians and their patients in an anonymous fashion and are free of bias because this study type is purely observational and retrospective.

The study objectives were:

- a) to assess the likely prevalence of rash in females less than forty years of age treated for CAP and AECB for longer than the intended treatment duration based upon existing patterns of antibiotic prescribing in the community, and
- b) to assess the effectiveness of restricting gemifloxacin presentation to fixed dosage packs as a risk management strategy.

The study assumed no patient education and no physician awareness of a treatment duration dependent adverse event. Indeed, unlike gemifloxacin, the drug selected for this analysis has no specific treatment duration restriction based on an increased frequency of adverse events associated with prolonged duration of therapy.

The antibiotic selected for this study was azithromycin (Zithromax[®]). It is indicated for both CAP and AECB and is available in both fixed dose pack and tablet forms. It is extensively used of the treatment of lower respiratory tract infections. There have been no recent changes in the indicated duration of therapy with this agent for either indication.

Methods

Primary data for the study were collected from Verispan, a division of Quintiles Transnational, a professional services firm specializing in healthcare and biotechnology. Using its health system interaction database, which contains data for 150+ million individuals in the US drawn from 58,000 pharmacies, 640,000 physicians, and 275 million annual medical claims, Verispan provided 8 week's worth of prescription data for individuals who were newly diagnosed with CAP or AECB between 12/1/01 and 3/31/02. All patients with complete records in the Verispan database who met the following criteria were tracked:

- a) the patient's records included a physician documented ICD-9 code indicative of CAP or AECB as shown in table 1

Table 1

ICD-9	Description
491	Chronic Bronchitis
491.0	Simple Chronic Bronchitis
491.1	Mucopurulent Chronic Bronchitis
491.2	Obstructive Chronic Bronchitis
491.20	Obstructive Chronic Bronchitis Without Mention of Acute Exacerbation
491.21	Obstructive Chronic Bronchitis With Acute Exacerbation
491.8	Other Chronic Bronchitis
491.9	Unspecified Chronic Bronchitis
ICD-9	Description
480	Viral Pneumonia
481	Pneumococcal Pneumonia
482.2	Pneumonia Due to Haemophilus influenzae
482.84	Legionnaire's Disease
483	Pneumonia Due to Specified Organism
483.1	Pneumonia Due to Chlamydia

- b) the patient was prescribed the predefined antibiotic of interest, azithromycin, in either a fixed dose pack, "Z pak", or in tablet or capsule form (250mg). Both initial and refill prescription information were recorded for each patient over a 4 week follow up period. Based on these criteria, the initial dosing and refill behaviors of a total of 4,876 AECB and 290 CAP patients were tracked.

- c) the patient (defined as "new start") had no history of fills in the Verispan Rx database for any of the following products within the 180 days prior to the start of the therapy episode: azithromycin, levofloxacin, gatifloxacin or moxifloxacin.

The ages of the patients were not recorded, so the age incidences of CAP and AECB were estimated based on three years of Scott-Levin physician drug and diagnosis audit use data as shown in table 2.

Table 2: Key RTI Antibiotic Use by Age

		0-18	19-40	41-45	46-59	60+	Unspecified	Adult Rx to Persons Less Than 40 Yrs of Age/All Adult Rx
AECB	%	18.64%	26.40%	7.75%	18.90%	25.74%	2.57%	33.49%
	n =	10,602,804.8	15,016,848	4,408,355	10,750,698	14,641,426.8	1,461,867.4	
CAP	%	21.69%	14.32%	4.91%	14.21%	42.46%	2.41%	18.86%
	n =	5,048,998.2	3,333,409.6	1,142,949.8	3,307,803.8	9,883,838.8	560,999.8	

3 Year Average of Drug Uses (3/00-3/02) for CAP and AECB as reported by Scott-Levin. "Key Antibiotics" include all quinilones, macrolide, cephalosporins, and aminopenicillins, plus erythromycin, sulfonamides, aminoglycosides, oxazolidinones, and tetracycline. 3 yr n = 56,882,000 for AECB and 23,278,000 for CAP.

The study incorporated the following key assumptions:

- a) any initial prescription for greater than the labeled duration of therapy for azithromycin is counted as equivalent to giving 10 days of therapy with gemifloxacin;
- b) any prescription refill within a 4 week period, following initial treatment, is considered equivalent to 10 days continuous therapy with gemifloxacin;
- c) 50% of the AECB and CAP populations are female; and
- d) 35.1% of females less than 40 years of age experience a rash with a prolonged duration of gemifloxacin therapy (greater than 7 days). Study 344 suggested a rate of 31.7%; the 35.1% used in this study is the upper limit of the 95% confidence interval constructed using the more conservative exact method.

These assumptions represent the most conservative estimate for the off label usage of gemifloxacin and its consequences for this population.

Appropriate treatment duration with azithromycin was defined as 5 days therapy for both CAP and AECB.

Results

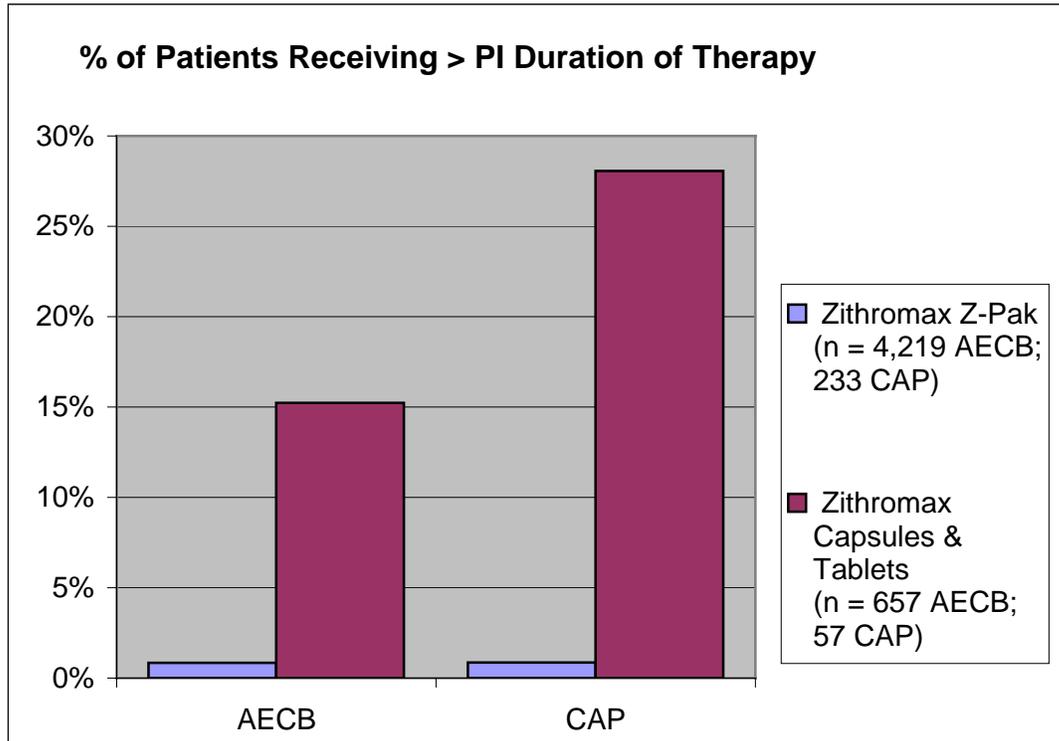
The prescribing of an initial treatment course for longer than the approved duration of therapy was uncommon with azithromycin fixed packs (Z-Pak) for both AECB and CAP, 0.85% and 0.86%, respectively, but was more frequent with prescriptions of tablets, 15.27% and 28.07%, respectively (Table 3 and Figure 1).

Table 3: Individuals Receiving Initial Zithromax® Course for Longer than the Indicated Duration of Therapy in the Product Insert (PI)

Dosage Form	AECB			CAP		
	Total Scripts #	> PI duration #	%	Total Scripts #	> PI duration #	%
Zithromax Z-Pak	4,219	36	0.85%	233	2	0.86%
Zithromax Cap (250 mg)	2	0	0.00%	0	0	0.00%
Zithromax Tab (250 mg)*	655	100	15.27%	57	16	28.07%
Totals	4,876	136	2.79%	290	18	6.21%

*13 AECB records included in the refill analysis were excluded here due to inconsistent information in the duration of therapy database (e.g. days supply = 0, pills dispensed = 6).

Figure 1



The prescription refill rates for AECB and CAP over a 27 day period following the initial prescription are shown in Tables 4 and 5, respectively. Refill rates for AECB were the same for both fixed dose and tablets and capsules. The refill rate for CAP within the same time period was higher than for AECB. The fixed dose refill rate was slightly higher than the refill rate for tablets and capsules, 9% versus 6.5%, respectively.

Table 4: Individuals Diagnosed with AECB Receiving Refills Within 27 Days of Initiating Therapy

Dosage Form	# of Initial Scripts	Number of Refills Post Initial Treatment				Total Within 27 Days # (%)
		1-6 days	7-13 days	14-20 days	21-27 days	
Zithromax Z-Pak	4,219	60	80	60	50	250 (5.9%)
Zithromax Capsules or Tablets	670	19	10	2	11	42 (6.3%)

Table 5: Individuals Diagnosed with CAP Receiving Refills Within 27 Days of Initiating Therapy

Dosage Form	# of Initial Scripts	Number of Refills Post Initial Treatment				Total Within 27 Days # (%)
		1-6 days	7-13 days	14-20 days	21-27 days	
Zithromax Z-Pak	233	5	5	5	6	21 (9.0%)
Zithromax Capsules or Tablets	57	1	0	0	0	1 (1.8%)

The impact of the frequency of therapy beyond the labeled indication, refill frequency within 27 days of initial therapy, and age and gender demography, for the indications AECB and CAP, assuming a 35.1% rash rate, are modeled in Table 6.

Table 6: Summary Rash Risk Analysis

	AECB		CAP	
	Fixed dose	Capsules & Tablets	Fixed dose	Capsules & Tablets
patients receiving initial prescription for longer than the package insert duration	0.85%	15.22%	0.86%	28.07%
patients getting refills within 27 days of initial script	5.93%	6.27%	9.01%	1.75%
total patients receiving greater than the labeled duration of therapy	6.78%	21.49%	9.87%	29.82%
(x) % of scripts written to adults < 40 years of age ¹ =	2.27%	7.20%	1.86%	5.62%
(x) % of scripts dispensed to females < 40 years of age (50%) =	1.13%	3.60%	0.93%	2.81%
(x) highest % of female < 40 rash at risk for rash (35.1%) = estimated % of total patient population at risk for rash	0.40%	1.26%	0.33%	0.99%

¹ Uses % calculated in table 2. AECB = 33.49%. CAP = 18.86%

The modeled rash rate in females less than 40 years of age receiving gemifloxacin for greater than 7 days based on the azithromycin data collected in this retrospective antibiotic utilization study are 0.40% and 0.33% in AECB and CAP, respectively, for the fixed dose pack. Limiting

physician choice to fixed dose packs for gemifloxacin would appear to reduce the rash rate by approximately 3 fold compared to making available bottles of tablets and capsules.

Conclusion

Azithromycin prescribing patterns provide a relevant and conservative model for likely gemifloxacin prescribing in CAP and AECB. The anticipated rash prevalence for females less than 40 years of age receiving gemifloxacin for greater than 7 days, within the overall treatment population is anticipated to be very low, 0.40% and 0.33% for the fixed dose pack and 1.26% and .99% for the bottles of tables/capsules in AECB and CAP, respectively. These results may appear somewhat surprising given the apparently high rash rate in this subgroup, however this subgroup has a relatively low prevalence of CAP and AECB disease. This analysis assumes no patient education & no physician awareness of duration of treatment associated rash with gemifloxacin. Consequently this represents a worse case scenario, in reality both patient education and clear physician guidance would be provided in the Product insert for gemifloxacin and would likely reduce this rash rate further.

The analysis of fixed dose pack usage versus usage of bottles of tablets and capsules suggests that deployment of fixed dose packs have a significant and positive impact on compliance with the Product insert in terms of length of the initial course of therapy, compared to prescriptions for bottles of tablets or capsules. Less than 1% of AECB and CAP patients prescribed fixed dose packs were prescribed longer than the intended treatment duration. By contrast 15% and 28% of patients treated for AECB and CAP respectively were prescribed longer than the intended treatment duration with bottles of tablets. Fixed dose packs had no impact on reducing refill rates compared to bottles within 27 days of initial prescription, and the rates were similar for both fixed dose packs and bottles of tablets or capsules.

This study puts in context the rash rate observed in the enriched population 344 study and its impact in the overall usage of gemifloxacin for the two target indications in the "real world" situation. The anticipated rash prevalence, as a consequence of extended duration of therapy with gemifloxacin, in this subpopulation for the treatment of CAP and AECB is very low. Ensuring that only a fixed dosage pack of gemifloxacin is available in the community is likely to be an effective risk management strategy to reduce prescribing of extended durations of gemifloxacin.